

Phase II Trial of Oral Cyclophosphamide, Prednisone, and Diethylstilbestrol for Androgen-Independent Prostate Carcinoma

Beth Hellerstedt, M.D.¹
 Kenneth J. Pienta, M.D.^{1,2}
 Bruce G. Redman, D.O.^{1,2}
 Peg Esper, M.S.N.¹
 Rodney Dunn, M.S.²
 Judith Fardig, PA-C¹
 Karin Olson, PA-C¹
 David C. Smith, M.D.^{1,2}

¹ Department of Internal Medicine, Division of Hematology/Oncology, University of Michigan School of Medicine, Ann Arbor, Michigan.

² University of Michigan Comprehensive Cancer Center, University of Michigan, Ann Arbor, Michigan.

Supported in part by Grant 2P30 CA 46592-14 from the National Cancer Institute and the National Institutes of Health.

Address for reprints: David C. Smith, M.D., University of Michigan Health System, 7302 CCGC 0946, 1500 E. Medical Center Drive, Ann Arbor, MI 48109; Fax: (734) 615-2719; E-mail: dcsmith@umich.edu

Received April 15, 2003; revision received July 10, 2002; accepted July 11, 2003.

© 2003 American Cancer Society
 DOI 10.1002/cncr.11686

BACKGROUND. The authors evaluated the combination of oral cyclophosphamide, oral prednisone, and diethylstilbestrol (DES) in patients with androgen-independent prostate carcinoma (AIPC).

METHODS. Thirty-seven patients with prostate carcinoma refractory to androgen ablation who had undergone antiandrogen withdrawal (if previously treated with an antiandrogen) were enrolled in the current study. They were treated with oral cyclophosphamide 100 mg per day on Days 1–20, prednisone 10 mg per day continuously, and DES 1 mg continuously, on a 30-day cycle. Warfarin 1 mg per day was given as prophylaxis for thrombosis. Patient levels of prostate-specific antigen (PSA) were monitored on a monthly basis, with imaging studies every 3 months. Patients continued to receive therapy until disease progression or the occurrence of significant toxicity. The effect of therapy on the patient's quality of life was assessed using the Functional Assessment of Cancer Therapy–Prostate.

RESULTS. Thirty-six patients were evaluable for response. Of the 36 patients, 15 (42%) had a 50% or greater decline in PSA levels from pretreatment levels and 1 patient (6%) with measurable disease had a partial response to therapy. The median duration of response was 4.5 months (range, 4–18 months). The overall median survival period was 16.4 months. The treatment was well tolerated, with only three patients removed from the study for toxicities associated with treatment. One patient, who had been treated for more than 24 months, developed acute leukemia. Quality of life evaluation in 17 patients showed a significant improvement in responders, whereas nonresponders had no deterioration while receiving therapy.

CONCLUSIONS. Cyclophosphamide, prednisone, and DES represent a well tolerated, low-cost combination therapy with significant activity in the treatment of patients with AIPC. *Cancer* 2003;98:1603–10. © 2003 American Cancer Society.

KEYWORDS: androgen-independent prostate carcinoma cyclophosphamide, prednisone, diethylstilbestrol.

Androgen-independent prostate carcinoma (AIPC) remains an incurable disease. Although AIPC previously was considered to be chemotherapy-resistant, new drugs and combinations have shown promise in the treatment of this disease.¹ However, more aggressive treatment can be associated with a higher incidence of treatment-related morbidity, which often is tolerated poorly in older patients. Therefore, lower-toxicity combinations are needed.

Diethylstilbestrol (DES) is an estrogen that has been used extensively in the treatment of hormone-dependent prostate carcinoma. In addition to its estrogenic properties, DES may have direct cytotoxic effects, which are potentially estrogen receptor-independent.² Multi-

ple reports have demonstrated the efficacy of DES as a first-line hormonal agent. The overall survival of patients treated with DES was similar to that seen with orchiectomy³⁻⁵ and lutenizing hormone-releasing hormone (LHRH) agonists.⁶⁻⁹ However, treatment-related mortality due to significant cardiovascular toxicity led most practitioners to abandon the drug. In these trials, DES was administered at 3-5 mg orally per day, as this was the dose considered to reliably provide castrate levels of testosterone.^{10,11} Other studies demonstrated that DES at 1 mg daily provided equal efficacy with fewer thromboembolic events.^{12,13}

The low cost of DES and the ease of oral administration prompted its reevaluation as a secondary hormonal agent. Smith et al.¹⁴ conducted a Phase II trial using 1 mg DES daily in patients with AIPC. The response rate was 43% using prostate-specific antigen (PSA) criteria (defined as a decrease in 2 successive measurements of PSA of greater than 50% from baseline). Only 5% of patients had thromboembolic complications. Another trial involving DES at 1 mg per day in combination with hydrocortisone (40 mg per day) and low-dose aspirin (75 mg per day) demonstrated a PSA response rate of 38%.¹⁵ In that study, 83% of symptomatic patients experienced a significant improvement in quality of life.

Cyclophosphamide was among the first chemotherapeutic agents to be tested in patients with AIPC. Intravenous cyclophosphamide showed modest efficacy, with response rates in the 10-20% range as a single agent¹⁶ and in the 30-50% range in combination therapy with doxorubicin.^{17,18} Cyclophosphamide, methotrexate, and 5-fluorouracil;¹⁹⁻²¹ cyclophosphamide, doxorubicin, and methotrexate;²² cyclophosphamide, cisplatin, and 5-fluorouracil;²³ and 5-fluorouracil, doxorubicin, and mitomycin C²⁴ did not show significant improvements in overall survival or response rates compared with cyclophosphamide alone.

Cyclophosphamide is well absorbed when given orally, with good bioavailability, resulting in levels comparable to those seen after intravenous administration.²⁵ Oral therapy has the added advantages of decreased toxicity and ease of administration. Initial results with oral cyclophosphamide in prostate carcinoma were disappointing when the drug was used in schedules designed to simulate bolus intravenous therapy.²¹ However, when given on a low-dose, intermittent schedule, oral cyclophosphamide produced more promising results, with PSA response rates of 30-35%.²⁶ Improvements in performance status and pain control also were noted.^{27,28}

Prednisone as a single agent also has shown efficacy in the treatment of AIPC. In a Phase III study

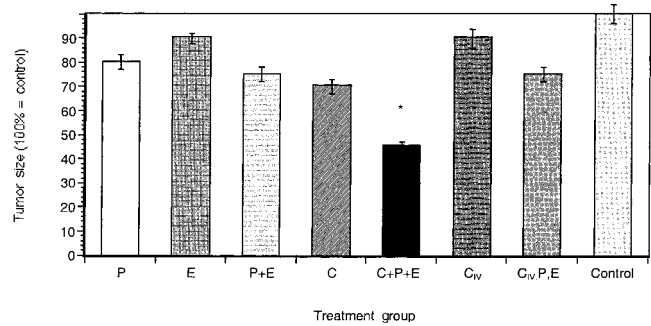


FIGURE 1. Animals were implanted with 200,000 MAT-Ly Lu cells. 10 animals per group, on Day 0 and sacrificed on Day 14. Oral drug treatments started on Day 1. Tumors were excised and weighed on Day 14. Group 1 (P) was treated with oral prednisone 0.3 mg daily (gavage). Group 2 (E) was treated orally with esterified estrogens 0.03 mg daily. Group 3 (P + E) was treated orally with steroid and estrogen. Group 4 (C) was treated with oral cyclophosphamide 3 mg per day. Group 5 (C + P + E) was treated with oral cyclophosphamide, steroid, and estrogen daily. Group 6 (C_{iv}) was treated with 30 mg intravenous cyclophosphamide on Days 4 and 11. Group 7 (C_{iv}, P, E) was treated with intravenous cyclophosphamide on Days 4 and 11 and treated orally with steroid and estrogen daily. Group 8 (control) consisted of untreated control animals. The group treated with a combination of oral cyclophosphamide, steroid, and estrogen demonstrated a significant decrease in tumor weight compared with control ($P < 0.001$).

comparing mitoxantrone and prednisone with prednisone alone, the primary endpoint of palliative response was seen in 21% of patients treated with prednisone alone.²⁹ In a second Phase III trial comparing flutamide with prednisone, prednisone therapy was associated with a subjective response rate of 56% and a PSA response rate of 21%, both of which were similar to the results achieved with flutamide treatment.³⁰ No differences were seen between the two treatments in time to progression or overall survival.

Given the efficacy of these agents, along with the relatively low and nonoverlapping toxicities, we explored the activity of oral cyclophosphamide, prednisone, and estrogen in the Dunning rat adenocarcinoma model. Animals were divided into seven groups and treated with different combinations of the three drugs. The group treated with the oral three-agent regimen had significantly smaller tumors compared with the other six groups (Fig. 1).

Based on these clinical and laboratory data, we designed a Phase II trial using the combination of oral cyclophosphamide, prednisone, and DES (CPD) in the treatment of AIPC. Because this combination included well-established drugs with nonoverlapping toxicities, we did not believe it was necessary to conduct a Phase I trial before proceeding with the current study, which

was designed to assess both the efficacy and impact on quality of life of this regimen.

MATERIALS AND METHODS

Preclinical Studies

Materials

Cyclophosphamide was obtained from Sigma (St. Louis, MO). Esterified estrogens and prednisone were obtained from the outpatient pharmacy of the University of Michigan (Ann Arbor, MI). All were prepared as sterile stock solutions of 1 mg/mL normal saline and stored at 4 °C.

Cell culture

The metastatic MAT-LyLu (MLL) subline of the Dunning R-3327 rat prostate adenocarcinoma line was obtained from Dr. John Isaacs (Johns Hopkins University, Baltimore, MD). MLL cells were grown and maintained in RPMI 1640 (Sigma-Aldrich, St. Louis, MO) medium containing 10% fetal bovine serum and 250 nM dexamethasone.

Animals

Male Copenhagen rats (200 g) were obtained from Harlan Sprague-Dawley (Indianapolis, IN). Methoxyflurane (Pittman-Moore, Washington Crossing, NJ) was used as inhalation anesthetic for injections and surgical procedures that were performed according to approved University of Michigan protocols.

Experimental treatment

Animals, 10 per group, were injected with 1×10^6 MLL cells subcutaneously into the flank on Day 0, based on a protocol approved by the University of Michigan Animal Investigation Committee. Animals were implanted with 1×10^6 MLL cells, 10 animals per group, on Day 0 and killed on Day 14. Oral drug treatments started on Day 1. Tumors were excised and weighed on Day 14. Group 1 was treated with oral prednisone 0.3 mg daily (gavage). Group 2 was treated orally with estrogen in the form of Estratabs 0.03 mg daily. Group 3 was treated orally with steroid and estrogen. Group 4 was treated orally with cyclophosphamide 3 mg per day. Group 5 was treated orally with cyclophosphamide, steroid, and estrogen every day. Group 6 was treated with 30 mg intravenous cyclophosphamide on Days 4 and 11. Group 7 was treated with intravenous cyclophosphamide on Days 4 and 11 and with oral steroid and estrogen daily. Group 8 consisted of untreated control animals. Tumor size was followed by caliper measurements along two axes and by final tumor weight when animals were killed by carbon dioxide inhalation euthanasia on Day 14.

Statistics

Statistical significance was determined using the Student *t* test as well as analysis of variance with Statgraphics software (Version 5.0; STSC, Rockville, MD).

Patients

Eligible patients were required to have a histologic diagnosis of adenocarcinoma of the prostate with progressive disease on hormone therapy. All patients who had not undergone orchiectomy underwent primary androgen suppression using an LHRH agonist. All patients receiving antiandrogen therapy at the time of progression underwent antiandrogen withdrawal, with evidence of disease progression after cessation of the antiandrogen. Patients were required to have a performance status of 2 or better on the Zubrod scale, along with a life expectancy of 12 weeks or more and adequate bone marrow (absolute neutrophil count $\geq 1500/\text{mm}^3$ and platelet count of $\geq 100,000/\text{mm}^3$), renal (creatinine level ≤ 1.3 mg/dL), and hepatic function (bilirubin level ≤ 1.6 mg/dL and an aspartate aminotransferase level ≤ 3 times the upper limit of normal). Patients were required to have either measurable soft tissue disease or evaluable disease (osseous disease with increasing levels of PSA or increasing levels of PSA alone). Patients were excluded from the study if there was evidence of brain metastases or spinal cord compression, untreated second malignancies, recent myocardial infarction, unstable angina, uncontrolled arrhythmia, valvular heart disease with decreased ejection fraction, uncontrolled hypertension, or history of deep venous thrombosis (DVT). To enter the study, patients were required to wait 4 weeks after the completion of any prior chemotherapy, biologic therapy, or radiotherapy. Written, informed consent was obtained from all patients in accordance with federal, state, and institutional guidelines.

Evaluations

Pretreatment evaluations consisted of a history and physical examination, complete blood count, serum chemistry profile, and PSA level measurement. Baseline imaging included a chest X-ray, a bone scan, and a computed tomography (CT) scan of the abdomen and pelvis. Complete blood counts and PSA levels were checked before each cycle of therapy. CT and bone scans, if positive at baseline, were repeated after every 3 cycles of therapy (90 days).

Quality of Life Evaluations

The Functional Assessment of Cancer Therapy–Prostate (FACT-P) was developed as a disease-specific quality of life instrument for patients with prostate

carcinoma. The general FACT is a 33-item instrument that measures quality of life using five subscales addressing physical well-being, social/family well-being, relationship with physician, emotional well-being, and functional well-being.³¹ The general FACT has demonstrated validity and reliability. The FACT-P subscale provides an additional 12 items that are specific to quality of life issues in men with prostate carcinoma, including sexuality, elimination, and comfort. The FACT-P was administered at baseline and monthly during therapy. Study participants completed the questionnaire before being evaluated by the clinical staff at each visit.

Treatment Regimen

All evaluations were performed in the outpatient clinic, and the medication was self-administered. Treatment consisted of cyclophosphamide administered daily at a dose of 100 mg orally on Days 1–20 of every 30-day cycle, prednisone 10 mg orally every day continuously, and DES 1 mg orally every day continuously. In addition, warfarin 1 mg orally every day also was given continuously to decrease the risk of DVT. Dose modification for cyclophosphamide was based on granulocyte and platelet counts from Day 21 of the preceding cycle. If anemia or thrombocytopenia developed, cyclophosphamide was held until the granulocyte count was 1500/mm³ or greater and the platelet count was 100,000/mm³ or greater. If the granulocyte count was less than 1000/mm³ or the platelet count was less than 50,000/mm³, all therapy was held until the toxicity resolved. When the bone marrow had recovered adequately, the dose of cyclophosphamide was decreased by 50% (to 50 mg per day) if the Day 21 granulocyte count was 1000–1499/mm³ and/or the Day 21 platelet count was 50,000–74,999/mm³. Therapy also was held for any toxicity worse than Grade 2 according to the National Cancer Institute Common Toxicity criteria. When the toxicity resolved to Grade < 2, cyclophosphamide was resumed at a dose of 50 mg per day. Subsequent cycles were given at full dose if there was no recurrence of toxicity. Patients were eligible to receive therapy indefinitely unless they had evidence of disease progression or a qualitatively unacceptable or life-threatening toxicity, were unable to comply with protocol requirements, or requested to stop receiving therapy.

Response Criteria

Response was assessed using standard criteria for measurable disease, if present. Complete response of bone-only disease required the disappearance of all measurable and evaluable lesions, with a decrease in serum levels of PSA to less than 0.1 ng/mL for at least

4 weeks. A partial response for measurable lesions was defined as a decrease below baseline of 50% or greater in the sum of the products of the perpendicular diameters of all measurable lesions. A partial response for PSA was defined as a 50% -or- greater decrease, lasting at least 4 weeks, from a given patient's baseline PSA level. Disease progression was defined as a 50% increase in PSA levels from nadir levels, a 25% increase or an increase of 10 cm² in the sum of the products of measurable lesion diameters, the appearance of any lesion that had disappeared or any new lesion, clear worsening of evaluable disease, or significantly increasing symptoms secondary to disease progression. All patients who did not meet these criteria were considered to have stable disease.

Statistical Considerations

The current study was designed to assess the efficacy of CPD, with a primary end point of tumor response. Response was assessed using serum PSA levels and measurable disease, if present. A Minimax two-stage accrual design provided 80% statistical power at the 5% significance level to assess the difference between the null response rate of 20% and the alternative response rate of 40%. The aim of the study was to determine whether the three-drug combination had a response rate similar to that of DES alone or that of the two-drug combination of cyclophosphamide and prednisone (both response rates were approximately 40% in Phase II trials). As such, the combination would not have been of further interest unless the response rate was at least that of its components. Kaplan–Meier methods were used to determine median survival times. The Student *t* test was used to assess differences in quality of life scores between responders and nonresponders.

RESULTS

Patient Characteristics

Between September 1998 and July 2001, 37 patients were enrolled in the current study. Patient characteristics are listed in Table 1. One patient was ineligible for the study secondary to evidence of chronic lymphocytic leukemia after entry laboratory studies were performed. This patient continued to receive the regimen and was followed for toxicity.

Of the remaining 36 patients, 15 previously had received treatment with chemotherapy. Three patients had received more than one regimen. The most common previous therapy was a combination of uracil with tegafur and leucovorin (*n* = 5), which was a previous study regimen at The University of Michigan Comprehensive Cancer Center. Other regimens included single-agent estramustine (*n* = 2), estramus-

TABLE 1
Patient Characteristics

No. enrolled	37
Age (yrs)	
Median (range)	66 (51–76)
Initial gleason score	
Median (range)	7 (5–9)
PSA at start of treatment	
Median (range)	63 (1.1–2021)
Disease status	
PSA only	4
Positive bone scan	17
Positive CT scan	6
Positive bone scan and CT scan	10
Previous treatment with chemotherapy (range of no. of regimens)	15 (0–2)

PSA: prostate-specific antigen; CT: computed tomography.

tine/etoposide ($n = 3$), cyclophosphamide/prednisone ($n = 1$), paclitaxel/estramustine/etoposide/cisplatin ($n = 2$), mitoxantrone/prednisone ($n = 2$), paclitaxel/estramustine/etoposide ($n = 3$), and vaccine therapy ($n = 1$). Sixteen patients had evidence of soft tissue disease before starting treatment, 27 had evidence of bone disease, 10 had both bone and soft tissue disease, and 4 had elevated PSA levels only.

Response

Thirty-six patients were assessable for response. Of the 36 patients, 15 (42%) had a greater-than-50% decline in PSA levels while receiving therapy, with 7 patients (19%) having a greater-than-75% decline. The median duration of response in patients with a greater-than-50% reduction in PSA level was 9 months. The median overall survival was 16.4 months.

Of the 15 patients with an initial PSA response, 3 were removed from the study due to disease progression as evidenced by a bone scan, 1 patient due to new measurable lesions as shown on CT scan, 3 patients due to PSA progression, and 5 patients due to toxicity or intolerance (1 thromboembolic event, 1 episode of urosepsis, 1 case of worsening lower-extremity edema, 1 case of breast tenderness, and 1 case of inability to travel to appointments). Three patients remained in the study without definable progression, 1 for 15 months and 2 for 18 months. Due to concerns about bladder and bone marrow toxicity, cyclophosphamide and prednisone were discontinued and these patients were maintained on DES alone.

Response was assessed by standard criteria in the 16 patients with bidimensional measurable disease. One patient had evidence of a partial response, and one patient demonstrated stable disease. Both pa-

TABLE 2
Toxicity Data

Toxicity	Grade 3	Grade 4
Neutropenia	0	0
Anemia	0	0
Thrombocytopenia	0	0
Lymphopenia	17	10
GI toxicity	0	0
Neuropathy	0	0
Thromboembolic toxicity	3 (1 popliteal DVT, 1 clot in AAA graft, 1 episode of atrial fibrillation)	1 (MI)

GI: gastrointestinal; DVT: deep venous thrombosis; AAA: abdominal aortic aneurysm MI: myocardial infarction.

tients had a PSA response, and neither had received previous chemotherapy.

Previous chemotherapy may have influenced response. For example, 4 of 15 patients (26%) who had received previous chemotherapy had a greater-than-50% decline in PSA levels, compared with 11 of 21 (52%) patients who had not received previous therapy. However, the pretreatment PSA level did not affect response, and nor did the presence or absence of lesions as demonstrated on CT or bone scan. Original Gleason score also did not appear to affect response, as PSA responses were seen in 3 of 9 (33%) patients with a score of 2–6, 4 of 9 (44%) patients with a score of 7, and 8 of 17 (47%) patients with a score of 8–10. The PSA response could be gradual, with time of maximal decrease in PSA levels ranging from 1 to 13 months. The median time to response was 2 cycles.

Toxicity

Two hundred cycles of therapy were delivered (range, 1–18 cycles). Toxicity is summarized in Table 2. Lymphopenia was the most common toxicity. Seventeen patients experienced Grade 3 lymphopenia, and 10 patients experienced Grade 4 decreases in lymphocyte counts. There were no episodes of Grade 3 or 4 granulocytopenia, thrombocytopenia, or anemia. Two patients developed spinal cord compression, one immediately after leaving the study secondary to an increasing PSA level and one during therapy. Four patients experienced cardiovascular toxicity, including myocardial infarction, ($n = 1$) popliteal DVT ($n = 1$), a clot in a previously placed abdominal aortic aneurysm graft ($n = 1$), and paroxysmal atrial fibrillation ($n = 1$). Other toxicities included a ureteral obstruction secondary to disease progression ($n = 1$) and an episode of urosepsis ($n = 1$). No patients required dose reduction for any reason while they were enrolled in the study.

Four patients were removed from the study for reasons other than defined toxicity criteria. One patient experienced worsening lower extremity edema of unknown cause but believed to be exacerbated by prednisone. A second patient had severe breast tenderness, a third had a severe increase in bone pain, and a fourth could not commit to the monthly clinic appointments called for by the protocol.

Study treatment was halted after 18 months for 3 patients who were still responding to therapy due to concern for the effects of long-term administration of cyclophosphamide. One of these patients was maintained on DES but experienced a prompt increase in his PSA level after a 6-month interval. He was restarted on the 3-drug combination but developed pancytopenia after 6 additional months of therapy. A bone marrow biopsy revealed blasts consistent with acute promyelocytic leukemia, which was confirmed by cytogenetics. At the time of the current report, this patient is undergoing induction chemotherapy.

Quality of Life

Seventeen patients were evaluable for quality of life assessment, including nine patients who responded to treatment and eight nonresponders. Baseline FACT-P scores were 120 and 122.6 for nonresponders and responders, respectively. There was a significant improvement in the scores of the group of patients responding to treatment between the baseline and first time point. Data were available at these time points for all nine responding patients. Mean FACT-P scores were 122.6 at baseline and 133 after the first time point ($P < 0.03$). Progressive disease was associated with a decline in quality of life scores. Data were available for eight patients at the off-treatment time point. The difference between mean FACT-P scores from Time Point 2 to the off-treatment time point was significant (from 133 to 126, $P < 0.05$). Finally, there was no significant difference between baseline and off-treatment FACT-P results for either responders or nonresponders, suggesting that the treatment itself did not result in a decline in the quality of life in either group.

DISCUSSION

Many recent trials have shown that chemotherapy for AIPC has significant efficacy in terms of PSA and even measurable disease response.^{1,32} However, because no overall survival benefit has been demonstrated in a Phase III trial, the need for more effective and less toxic therapy remains. All three components of this combination have demonstrated responses as single agents in the setting of AIPC. The current study demonstrates that the CPD combination also has significant activity, with sustained PSA responses. The low

incidence of side effects makes this an attractive combination for multiple clinical situations, ranging from the patient with a performance status of 100% who would like to avoid significant side effects to the patient with an impaired status who will not tolerate a more toxic regimen. Nonetheless, cardiovascular toxicity was documented in four patients, despite prophylactic low-dose warfarin administration. Quality of life evaluation during therapy showed no significant negative effects from this combination even in the absence of response, whereas responders had a significant improvement in quality of life scores while they were receiving therapy.

Despite the favorable toxicity profile, long-term administration of CPD probably is not a feasible option. As with all alkylating agents, cyclophosphamide may cause significant side effects even when given at low doses. Development of acute promyelocytic leukemia after administration of chemotherapy agents has been reported.³³ This risk appears to be directly related to the cumulative exposure to cyclophosphamide. The patient in the current study who developed acute leukemia after 24 months of therapy is typical of patients who develop this second malignancy. The risk of this complication must be weighed against the potential benefit when considering the use of CPD.

The PSA response rate associated with CPD is higher than that associated with cyclophosphamide or prednisone alone, but is similar to that associated with DES alone.^{13,14} It is unclear whether the response associated with the combination can be attributed solely to DES. In a previously published Phase II trial of DES as a single agent,¹⁴ 71% of patients were asymptomatic, with a median PSA level of 23.4. None of the patients in that study had been treated with chemotherapy, suggesting that they may have had less-advanced disease.

Response to CPD typically was of short duration, although a few patients demonstrated prolonged responses. Some patients were removed from the study secondary to meeting PSA criteria for progression even though their disease burden was clearly and significantly improved. For example, one patient's PSA level was 184.2 at study entry and reached a nadir level of 2.2, after 7 cycles of therapy. Although his PSA level was greater than 50% of his nadir level (i.e., > 3.3) in the subsequent cycle, the greater than 90% reduction in his PSA level and the lack of measurable disease demonstrate the potential impact of this combination.

A practical approach in future trials would be a randomization of patients to receive DES versus CPD. Sequential therapy with DES followed by cyclophosphamide and prednisone or CPD at the time of progression also may allow for a longer duration of re-

sponse with continued minimal toxicity. In clinical practice, this regimen may be an option for patients with symptomatic disease, although the current trial did not attempt to evaluate the impact of therapy on symptoms, including bone pain. Another option for future trials would be to assess the impact of CPD as maintenance therapy after response to one of the antimicrotubule regimens that are gaining popularity. Any such use, however, should be of short duration with careful attention to cumulative doses of cyclophosphamide.

In the current study, CPD is associated with a 42% PSA response rate in a series of patients with AIPC. CPD therapy generally was well tolerated, even in patients with marginal performance status. Further evaluation of this regimen as a palliative intervention or as short-term maintenance chemotherapy after response to more aggressive treatments is warranted.

REFERENCES

- Smith DC. Chemotherapy for hormone refractory prostate cancer. *Urol Clin North Am.* 1999;26:323–331.
- Robertson CN, Roberson KM, Padilla GM, et al. Induction of apoptosis by diethylstilbestrol in hormone-insensitive prostate cancer cells. *J Natl Cancer Inst.* 1996;88:908–917.
- VACURG. Treatment and survival of patients with cancer of the prostate. The Veterans Administration Co-operative Urological Research Group. *Surg Gynecol Obstet.* 1967;124:1011–1017.
- Blackard CE, Byar DP, Jordan WP Jr. Orchiectomy for advanced prostatic carcinoma. A reevaluation. *Urology.* 1973;1:553–560.
- Robinson MR, Smith PH, Richards B, Newling DW, de Pauw M, Sylvester R. The final analysis of the EORTC Genito-Urinary Tract Cancer Co-Operative Group Phase III clinical trial (protocol 30805) comparing orchidectomy, orchidectomy plus cyproterone acetate and low dose stilboestrol in the management of metastatic carcinoma of the prostate. *Eur Urol.* 1995;28:273–283.
- The Leuprolide Study Group. Leuprolide versus diethylstilbestrol for metastatic prostate cancer. *N Engl J Med.* 1984;311:1281–1286.
- Garnick MB. Leuprolide versus diethylstilbestrol for previously untreated Stage D2 prostate cancer. Results of a prospectively randomized trial. *Urology.* 1986;27(1 Suppl):21–28.
- Citrin DL, Résnick MI, Guinan P, et al. A comparison of Zoladex and DES in the treatment of advanced prostate cancer: results of a randomized, multicenter trial. *Prostate.* 1991;18:139–146.
- Waymont B, Lynch TH, Dunn JA, et al. Phase III randomised study of zoladex versus stilboestrol in the treatment of advanced prostate cancer. *Br J Urol.* 1992;69:614–620.
- Beck PH, McAnich JW, Goebel JL, Stutzman RE. Plasma testosterone in patients receiving diethylstilbestrol. *Urology.* 1978;11:157–160.
- Kent JR, Bischoff AJ, Arduino LJ, et al. Estrogen dosage and suppression of testosterone levels in patients with prostatic carcinoma. *J Urol.* 1973;109:858–860.
- Bailar JC III, Byar DP. Estrogen treatment for cancer of the prostate. Early results with 3 doses of diethylstilbestrol and placebo. *Cancer.* 1970;26:257–261.
- Byar DP, Corle DK. Hormone therapy for prostate cancer: results of the Veterans Administration Cooperative Urological Research Group studies. *NCI Monogr.* 1988;7:165–170.
- Smith DC, Redman BG, Flaherty LE, Li L, Strawderman M, Pienta KJ. A Phase II trial of oral diethylstilbestrol as a second-line hormonal agent in advanced prostate cancer. *Urology.* 1998;52:257–260.
- Farrugia D, Ansell W, Singh M, Philp T, Chinegwundoh F, Oliver RT. Stilboestrol plus adrenal suppression as salvage treatment for patients failing treatment with luteinizing hormone-releasing hormone analogues and orchidectomy. *BJU Int.* 2000;85:1069–1073.
- Kyaduno M, Yamaguchi S, Matsumiya K, Osafune M. Inter-mittent intravenous high-dose cyclophosphamide therapy in advanced prostatic cancer with distant metastasis. *Hinyokika Kyo.* 1989;11:1865–1869.
- Small EJ, Srinivas S, Egan B, McMillan A, Rearden TP. Doxorubicin and dose-escalated cyclophosphamide with granulocyte colony-stimulating factor for the treatment of hormone-resistant prostate cancer. *J Clin Oncol.* 1996;14:1617–1625.
- Stephens RL, Vaughn C, Lane M, et al. Adriamycin and cyclophosphamide versus hydroxyurea in advanced prostatic cancer. A randomized Southwest Oncology Group study. *Cancer.* 1984;53:406–410.
- Muss HB, Howard V, Richards F II, et al. Cyclophosphamide versus cyclophosphamide, methotrexate, and 5-fluorouracil in advanced prostatic cancer: a randomized trial. *Cancer.* 1981;47:1949–1953.
- Herr HW. Cyclophosphamide, methotrexate and 5-fluorouracil combination chemotherapy versus chloroethyl-cyclohexy-nitrosourea in the treatment of metastatic prostatic cancer. *J Urol.* 1982;127:462–465.
- Wozniak AJ, Blumenstein BA, Crawford ED, Boileau M, Rivkin SE, Fletcher WS. Cyclophosphamide, methotrexate, and 5-fluorouracil in the treatment of metastatic prostate cancer. A Southwest Oncology Group study. *Cancer.* 1993;71:3975–3978.
- Saxman S, Ansari R, Drasga R, et al. Phase III trial of cyclophosphamide versus cyclophosphamide, doxorubicin, and methotrexate in hormone-refractory prostatic cancer. A Hoosier Oncology Group study. *Cancer.* 1991;70:2488–2492.
- Murphy GP, Priore RL, Scardino PT. Hormone-refractory metastatic prostatic cancer treated with methotrexate, cyclophosphamide plus Adriamycin, cis-platinum plus 5-fluorouracil plus cyclophosphamide. National Prostatic Cancer Project randomized trial. *Urology.* 1988;32:33–40.
- Kasimis BS, Miller JB, Kaneshiro CA, Forbes KA, Moran EM, Metter GE. Cyclophosphamide versus 5-fluorouracil, doxorubicin, and mitomycin C (FAM) in the treatment of hormone-resistant metastatic carcinoma of the prostate: a preliminary report of a randomized trial. *J Clin Oncol.* 1985;3:385–392.
- Struck RF, Alberts DS, Horne K, Phillips JG, Peng YM, Roe DJ. Plasma pharmacokinetics of cyclophosphamide and its cytotoxic metabolites after intravenous versus oral administration in a randomized, crossover trial. *Cancer Res.* 1987;47:2723–2726.
- Abell FL, Wilkes JD, Divers L, Huben R, Velagapudi S, Raghavan D. Oral cyclophosphamide (CTX) for hormone refractory prostate cancer (HRPC) [abstract]. *Proc Am Soc Clin Oncol.* 1995;14:243.

27. Raghavan D, Cox K, Pearson BS, et al. Oral cyclophosphamide for the management of hormone-refractory prostate cancer. *Br J Urol*. 1993;72:625–628.
28. Maulard-Durdux C, Dufour B, Hennequin C, Chretien Y, Delanian S, Housset M. Phase II study of the oral cyclophosphamide and oral etoposide combination in hormone-refractory prostate carcinoma patients. *Cancer*. 1996;77:1144–1148.
29. Tannock IF, Osoba D, Stockler MR, et al. 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*. 1996;14:1756–1764.
30. Fossa SD, Slee PH, Brausi M, et al. Flutamide versus prednisone in patients with prostate cancer symptomatically progressing after androgen-ablative therapy: a Phase III study of the European Organization for Research and Treatment of Cancer Genitourinary Group. *J Clin Oncol*. 2001;19:62–71.
31. Esper PS, Pienta KJ, Cella D. FACT-P: a new instrument for quality of life evaluation in prostate cancer [abstract]. *J Urol*. 1995;153:42a.
32. Oh WK. Chemotherapy for patients with advanced prostate carcinoma: a new option for therapy. *Cancer*. 2000;88(12 Suppl):3015–3021.
33. Beaumont M, Sanz M, Carli PM, et al. Therapy-related acute promyelocytic leukemia. *J Clin Oncol*. 2003;21:2123–2137.