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# Androgen Priming and Cytotoxic Chemotherapy in Advanced Prostatic Cancer

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***Summary.*** *Hormone manipulation has been standard therapy for metastatic adenocarcinoma of the prostate for many years. Recently cytotoxic drugs have been studied, but their effectiveness has been limited, indicating the need for new therapeutic approaches. Based upon the hypothesis that cytotoxic drugs are most effective against actively proliferating cells, we have designed a clinical pilot study employing cyclical androgen priming to transiently stimulate tumor cells followed by cytotoxic chemotherapy with cyclophosphamide and methotrexate. There were nine responders (43%) out of 21 patients entered in the study, with a median duration of response that has not been reached at 9+ months. Survival was significantly better in responders than in non-responding patients. These results are similar to those of other studies in which chemotherapy was used alone. Chemotherapy toxicity with this schedule was mild. However, the androgen priming frequently resulted in increased bone pain, and there was one episode of spinal cord compression, suggesting that tumor stimulation was achieved. These results demonstrate the need for additional basic studies of the effects of testosterone on tumor cell kinetics before further clinical trials of this approach are initiated.*

## Introduction

Most patients with adenocarcinoma of the prostate gland either present with metastatic disease or will eventually develop evidence of distant metastases requiring systemic therapy. Hormone manipulation by orchiectomy or pharmacologic estrogen administration has been the standard therapy for several decades. Endocrine therapy provides important palliation of the symptoms of this disease, but patient survival is not prolonged dramatically [15]. Furthermore, treatment of primary endocrine failures with a secondary hormone therapy is rarely beneficial.

In the past decade studies of the effects of cytotoxic chemotherapy in patients with prostate cancer have been initiated. While this work is still incomplete, it has met with limited success [19]. Although response to therapy is extremely difficult to quantify in this disease, objective tumor regression is observed in only 10%–30% of patients treated with the most active agents. Furthermore, a significant survival advantage has not been observed for treated groups as a whole compared with those not receiving chemotherapy [19]. It is clear that exploration of new treatment approaches is warranted.

The relative resistance of human prostate cancer to cytotoxic drugs may be partially explained on a cell kinetic basis. These tumors are frequently indolent and progress slowly, suggesting that the majority of tumors have a low growth fraction. In addition, most patients with prostate cancer have received chemotherapy late in the course of their disease when the tumor burden is large, which may further reduce the growth fraction. Tumors with a small growth fraction may be relatively insensitive to drugs which are most effective against actively proliferating cells [4, 20]. Thus, cytotoxicity might be enhanced by increasing the tumor growth fraction or by synchronization of tumor cells into a particularly vulnerable phase of the cell cycle.

More than 20 years ago such a hypothesis provided the rationale for the combined use of $^{32}P$ administration following a 2-week course of testosterone to stimulate tumor cells in patients with advanced prostate cancer [1–3, 5, 8, 10, 14, 16, 17, 21]. The androgen priming was designed to increase the uptake of the isotope into the tumor or adjacent bone and, thereby, increase tumor cell kill. Although the regimen was effective in reducing pain in patients

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with prostate cancer metastatic to bone, the exact role of the androgen priming was not clear. However, the observation that bone pain actually increased during the administration of testosterone suggests that transient tumor stimulation was achieved.

We have recently designed a similar clinical pilot study employing cyclical androgen priming, to transiently stimulate tumor cells, followed by cytotoxic chemotherapy. This report summarizes the results of this trial.

## Methods

*Patient Population.* A total of 21 patients with advanced symptomatic stage $D_2$ adenocarcinoma of the prostate were entered on study between March 1979 and October 1980. Six patients are still living and have now been followed for 6, 9, 13, 27, 29, and 29 months. Patients with a serum creatinine of $\geq 3.0$ mg/dl and those with a total white blood cell count of $< 4{,}000/\mu l$ or platelet count $< 100{,}000/\mu l$ (unless clearly due to tumor involvement of the bone marrow) were not eligible for study. Patients who had received previous cytotoxic chemotherapy and those with suspected CNS or epidural involvement by tumor were also excluded.

Other characteristics of the patient population are shown in Table 1. The majority of patients were only partially ambulatory and all of them had extensive bone metastases. In addition to bone disease, two patients had lymph node involvement and two patients had visceral metastases (lung, and lung plus liver) that provided easily measurable sites of disease. Eighteen of the 21 patients had received previous endocrine therapy but had progressive disease upon entry into this study. Three patients were previously untreated except for local surgical procedures. Response in these patients was evaluated separately.

*Treatment Schedule.* Twelve patients had already undergone orchiectomy as a prior therapy for their disease. Eight of the remaining nine patients underwent orchiectomy as part of this study to lower the plasma testosterone to castrate levels. One patient refused orchiectomy and received DES 3 mg per day to suppress plasma testosterone.

After recovery from orchiectomy (14 days), and after careful neurological examination to exclude patients with possible CNS involvement, patients started intermittent cycles of androgen priming and cytotoxic chemotherapy (Table 2). A high physiologic replacement dose (5 mg PO b.i.d.) of fluoxymesterone was administered for 4 days in an attempt to transiently stimulate tumor DNA synthesis and metabolism. On day 3, cyclophosphamide, an active agent in prostate cancer [9], and methotrexate, a cell cycle S-phase-specific agent, were given. Standard dosage modifications were used in the event of renal, hematologic, mucosal, or bladder toxicity. Initial doses in patients who had previously received extensive pelvic irradiation were reduced: cyclophosphamide 500 mg/m$^2$ IV and methotrexate 30 mg/m$^2$ IV. Doses were escalated step-wise by 10% in the absence of significant toxicity. Four patients received only one cycle of treatment: treatment was discontinued in two patients because of toxicity (see below) and in two patients because of early death unrelated to therapy. Seventeen patients received at least two cycles of treatment (range 2–24). Due to the inherent potential morbidity associated with prolonged chemotherapy, therapy is stopped after 2 years of treatment. Subsequent therapy in patients progressing on study included phase I or II chemotherapy agents (7 patients), radiation therapy (5 patients) or $^{32}P$ (1 patient).

**Table 1.** Patient characteristics

| | | |
|---|---|---|
| Total patients | 21 | |
| Median age (range) | 65 | (49 – 74) |
| Performance status | | |
| 0–1 (fully ambulatory) | 7 | |
| 2 (> 50% ambulatory) | 6 | |
| 3 (< 50% ambulatory) | 7 | |
| 4 (bedridden) | 1 | |
| Sites of metastatic disease | | |
| Bone only | 17 | |
| Bone + lymph node | 2 | |
| Bone + viscera | 2 | |
| Elevated acid phosphatase | 14 | |
| Previous therapy | | |
| None | 3 | |
| Endocrine | 18 | |
| Orchiectomy | 12 | |
| DES[a] | 15 | |
| Radiation[b] | 5 | |

[a] One patient received TACE and another Megace rather than DES

[b] Radiation to sites of metastatic bone disease

**Table 2.** Treatment regimen[a]

| | | |
|---|---|---|
| Fluoxymesterone | 5 mg PO b.i.d. | Days 1–4 |
| Cyclophosphamide | 600 mg/m$^2$ IV | Day 3 |
| Methotrexate | 40 mg/m$^2$ IV | Day 3 |

[a] Cycles are repeated every 3 weeks

*Treatment Evaluation and Response Criteria.* Pretreatment evaluation in all patients included a history, physical examination, estimation of performance status, body weight, complete blood count, platelet count, serum acid phosphatase (prostatic fraction), alkaline phosphatase, lactate dehydrogenase, serum creatinine, chest X-ray, bone marrow aspiration and biopsy, intravenous pyelogram, bone scan, and skeletal X-ray survey. Liver scans were performed as indicated by physical findings or elevation in liver function tests. The hemogram and blood chemistry tests were repeated prior to each cycle of therapy. Roentgenograms and/or scans were repeated at 4-month intervals or earlier to document disease progression.

Response criteria for objective regression, stable disease, or disease progression were those of the National Prostatic Cancer Project [18]. Survival times were computed by the method of Kaplan and Meier [11], and comparisons were made according to the log rank analysis [13].

## Results

### *Response to Treatment*

Twenty-one patients were entered in this study. Four patients received one cycle of therapy or less due to early death (2) or toxicity (2), but all are included in the analysis. Forty-three percent of the patients responded to this combined-modality regimen (Ta-

**Table 3.** Response to therapy

| Patients (no.) | CR | PR | SD | Total (%) |
|---|---|---|---|---|
| Total (21) | 1 | 3 | 5 | 9 (43) |
| Previously untreated (3) | 1 | 2 | – | 3 (100) |
| Previously treated (18) | – | 1 | 5 | 6 (33) |

CR, complete remission; PR, partial remission; SD, stable disease

ble 3). Responses included one complete response, three partial responses, and stable disease in five patients. As expected, the three previously untreated patients responded well to therapy. The patient who enjoyed a complete response presented with bone metastases, lymphangitic lung metastases, liver metastases, a pelvic mass, elevated acid phosphatase, and significant weight loss. Treatment resulted in normalization of bone and liver scans, chest X-ray, acid phosphatase, and performance status. The pelvic mass disappeared and the patient gained more than 70 pounds in weight. Chemotherapy has recently been stopped after 2 years of treatment. Treatment was less effective in previously treated patients, and only 33% responded, including one patient with stable disease for more than 2 years. Chemotherapy has also been discontinued in this patient.

The duration of response for the nine responding patients ranged from 3 to 29+ months, with a median that has not been reached at 9+ months. The three previously untreated patients had response durations of 13+, 14, and 29+ months. Of the six previously treated patients who responded, one was lost to follow-up with disease stable at 6 months. Another patient, with stable disease continuing at 9 months, was taken off study because of the development of a second primary (squamous cell carcinoma of the lung). The remaining four previously treated patients responded for 3, 6, 7, and 27 months.

The median survival from the time of initiation of treatment for all patients entered on study was 10 months, with a range of 1–29 months. All 12 patients who did not respond to therapy have died, with a median survival of 7 months. When the previously treated patients are evaluated separately, the median survival for the responding and non-responding patients is 13+ and 7 months, respectively. Actuarial survival of the previously treated patients who responded was modestly superior to survival of those who did not respond (Fig. 1) ($P < 0.08$). Although the numbers are small, actuarial survival for the entire group of patients achieving CR and PR was similar to that for patients with stable disease (not shown).

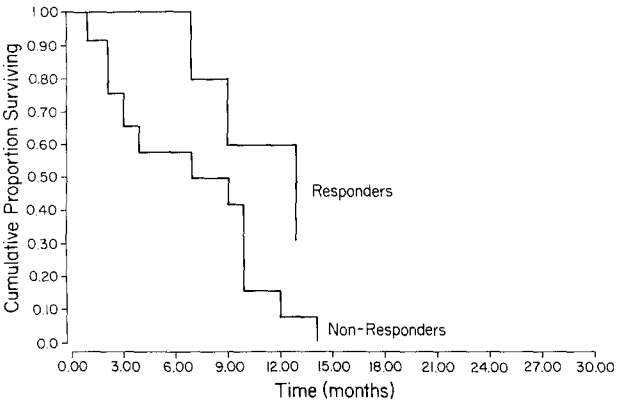


**Fig. 1.** Actuarial survival of 18 hormone-refractory patients treated with androgen priming and chemotherapy

*Toxicity*

In general, the therapy was well-tolerated and there were no treatment-related deaths with a median of six cycles of therapy given to the 21 patients (Table 4). The majority of patients had mild hematologic toxicity. One life-threatening infection occurred during leukopenia, but no episodes of bleeding due to thrombocytopenia were observed. Most patients (15) tolerated 100% of their prescribed initial dose of chemotherapy throughout their course of treatment. Nausea or vomiting (one severe) and mucositis (one severe) were each seen in five patients.

Three types of toxicity appeared to be related to the androgen priming. First, one patient developed an acute psychosis on the second day of administration of fluoxymesterone and was taken off study. The psychosis resolved and evaluation of the CNS by spinal puncture and CT scan was negative. Second, another patient developed spinal cord compression from a large epidural mass on day 2 of his second course of androgen priming. Early recognition and immediate decompression laminectomy resulted in normalization of bowel and bladder function and sensation, and in 75% return of motor function. In retrospect, this patient gave a history of new paresthesias in his left foot, which had been missed at the initial pretreatment examination. Third, ten patients had increased bone pain within 24–48 h after starting androgen priming. The pain was graded severe in two patients, moderate in three, and mild in five patients. The increased pain was controlled with increased analgesics, and resolved within 48–72 h of the completion of androgen priming. Therapy was discontinued in one patient with stable disease after seven cycles of treatment because of intolerable pain. This patient was scored as a non-responder. None of the three previously untreated patients had increased

**Table 4.** Toxicity of androgen priming and chemotherapy

| | No. of patients |
|---|---|
| Treatment-related death | 0 |
| Leukopenia (cells/μl) | |
| < 2000 | 5 |
| 2000–3000 | 4 |
| 3000–4000 | 6 |
| > 4000 | 6 |
| Thrombocytopenia (cells/μl) | |
| < 50,000 | 2 |
| 50,000–100,000 | 1 |
| > 100,000 | 18 |
| Nausea or vomiting | 5 |
| Mucositis | 5 |
| Acute psychosis | 1 |
| Spinal cord compression | 1 |
| Transient increase in pain | 10 |

pain during fluoxymesterone administration. In the previously treated group no relationship between response to chemotherapy and increased pain with androgen priming was observed.

## Discussion

In this pilot study transient androgen priming was used to deliberately stimulate tumor DNA synthesis and to recruit non-proliferating cells into the cell cycle, where they may be more vulnerable to cytotoxic agents. A similar program has been studied in the past with $^{32}P$ as the cytotoxic agent [1–3, 5, 8, 10, 14, 16, 17, 21]. In these studies increased pain was noted early in the androgen priming, suggesting that tumor stimulation might only require brief androgen exposure. Therefore, in our study the shorter duration was chosen to minimize the potential morbidity of prolonged tumor stimulation.

Our patient population included both previously untreated patients and patients who had previously undergone endocrine therapy. It could be argued that tumor cells in the latter group of patients might be hormone-independent, thus making these patients poor candidates for 'androgen priming'. However, the increased pain seen in ten of the 18 previously treated patients in our series, as well as that noted in the previous studies with androgen priming and $^{32}P$, suggests that many of these tumors may still be responsive to androgen.

Evaluation of potential toxicity was a major focus of this pilot study. The androgen priming itself could result in morbidity from tumor stimulation. In addition, androgen priming could enhance toxicity from the cytotoxic drugs by stimulating DNA synthesis in normal, potentially androgen-sensitive cells such as bone marrow. However, chemotherapy toxicity in this study was mild and did not appear to be exaggerated by the priming. Hematologic toxicity was minimal in most patients, and significant mucositis was rare.

The major toxicity observed in this study was related to the androgen priming itself. A transient increase in bone pain was common, often requiring modification of pain medication. One patient was withdrawn from the study because of poorly controlled pain. Increased pain was more common in previously treated patients with poor performance status, and presumably a larger tumor burden. The development of increased pain concomitant with androgen administration, and its rapid resolution after discontinuation of androgen, suggest that a blood level of androgen sufficient for tumor stimulation was achieved.

The most serious complication was the development of acute spinal cord compression in one patient during his second cycle of androgen priming. In retrospect this patient had subtle manifestations of cord compression that, if recognized, would have made him ineligible for study. Because these patients were hospitalized during each cycle of therapy specifically to monitor for such complications, this patient's condition was recognized and treated promptly, with good return of function. Although spinal cord compression is a relatively frequent complication in patients with prostate cancer, the development of this syndrome during androgen priming is quite uncommon. In 11 studies including ours [1–3, 5, 8, 10, 14, 16, 17, 21], only eight of 192 patients with advanced prostate cancer developed symptoms of cord compression. Furthermore, several of these patients had evidence of cord compression prior to the administration of androgen. Nevertheless, careful selection and close monitoring of patients is necessary during androgen priming to avoid this potential complication.

The response to treatment in this pilot study is similar to that reported in other published studies of chemotherapy alone in patients with advanced prostate cancer [19]. The three previously untreated patients, whom we included primarily to evaluate toxicity in patients with good performance status, all responded well and had minimal toxicity. Obviously it is impossible in this small study to decipher the relative roles of orchiectomy, chemotherapy, and androgen priming in this group of patients.

A critical feature of further studies of this treatment approach will be to determine whether the desired cell kinetic effect has been achieved, and to determine the most appropriate sequence of hor-

mone priming and chemotherapy. The increased pain and the development of cord compression in patients receiving androgen priming suggest that stimulation of tumor cell proliferation occurs in certain patients. However, local edema, an effect on non-tumor elements such as bone or stroma, or a hypertrophic rather than hyperplastic effect on the tumor itself could also explain these clinical observations. Furthermore, although long-term testosterone administration is usually associated with evidence of increased tumor growth, in an occasional patient with prostatic cancer there may actually be a beneficial effect [6], emphasizing the need to confirm the biological effect of androgen priming on the prostate cancer cells. During this study we attempted to determine the tritiated thymidine labeling index as an estimate of the fraction of tumor cells in S-phase. However, we have been unsuccessful in preparing a tumor cell suspension from bone marrow biopsy specimens even when the bone marrow is extensively replaced. Other cell kinetic techniques need to be developed for this disease, in which repeated tumor sampling is difficult.

In summary, we have completed a pilot study of transient androgen priming combined with cytotoxic drugs in an attempt to improve the treatment of patients with advanced prostate cancer. The regimen used has acceptable chemotherapy toxicity, but the androgen therapy may be associated with significant morbidity. Furthermore, the therapeutic results are no better than one might expect from the cytotoxic drugs used alone. Cell kinetic studies are required to better define the effects of androgen priming before future clinical trials of this approach are initiated. However, recent reports of the effectiveness of this strategy in an animal model and in another clinical trial [7, 12] suggest that further clinical and laboratory studies are warranted.

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