Effects of Intermittent Androgen Suppression on Androgen-Dependent Tumors

Apoptosis and Serum Prostate-Specific Antigen

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Background. **Since postcastration progression of tumors to an androgen-independent state appears to be linked to the cessation of androgen-induced differentiation of tumorigenic stem cells, the authors hypothesized that the replacement of androgens at the end of a period of apoptotic regression might result in the regeneration of differentiated tumor cells with further apoptotic potential.**

Methods and Results. **To determine the effect of intermittent exposure of androgens on the androgen-dependent Shionogi carcinoma, the tumor was transplanted into a succession of male mice, each of which was castrated when the estimated tumor weight became about 3 g. After the tumor had regressed to 30% of the original weight, it was transplanted into the next noncastrated male. This cycle of transplantation and castration-induced apoptosis was repeated successfully four times before growth became androgen-independent during the fifth cycle. In four of Stage C and three of Stage D patients with prostate cancer, androgen withdrawal was initiated with cyproterone acetate (100 mg/d) and diethylstilbestrol (0.1 mg/d) and then maintained with cyproterone acetate in combination with the luteinizing hormone-releasing hormone agonist, goserelin acetate (3.6 mg/month). After 6 or more months of suppression of serum prostate-specific antigen (PSA) into the normal range, treatment was interrupted for 2 to 11 months. After recovery of testicular function, androgen-withdrawal therapy was resumed when serum PSA increased to a level of about 20 μg/l. This cycle was repeated sequentially to a total of two to four times over treatment periods of 21 to 47 months with no loss of androgen dependence.**

Conclusions. **These results demonstrate that intermittent androgen suppression can be used to induce multiple apoptotic regressions of a tumor; they also suggest that the cyclic effects of such treatment on prostate cancer can be followed by the sequential measurement of serum PSA levels.** ***Cancer*** **1993; 71:2782–90.**

Key words: intermittent androgen suppression, prostate, Shionogi carcinoma, apoptosis, prostate-specific antigen.

Apoptotic regression of an androgen-dependent tumor can be induced by any procedure which reduces the intracellular concentration of dihydrotestosterone by 80% or more.[1,2] The benefit of such therapy usually is temporary, despite a high initial response rate, owing to the fact that surviving tumor cells generally progress to an androgen-independent condition.[3–5] In studying progression of the androgen-dependent Shionogi carcinoma, we found previously that androgen withdrawal alters the ratio of stem cells in the tumor cell population, as shown in Figure 1.[6] During the initial apoptotic phase, the changes include the elimination of differentiated cells and a decrease in the proportion of tumorigenic stem cells. With progression and recurrence, a marked 20-fold increase in the proportion of total stem cells (Fig. 1) and a massive 500-fold increase in the proportion of androgen-independent stem cells[6] are observed.

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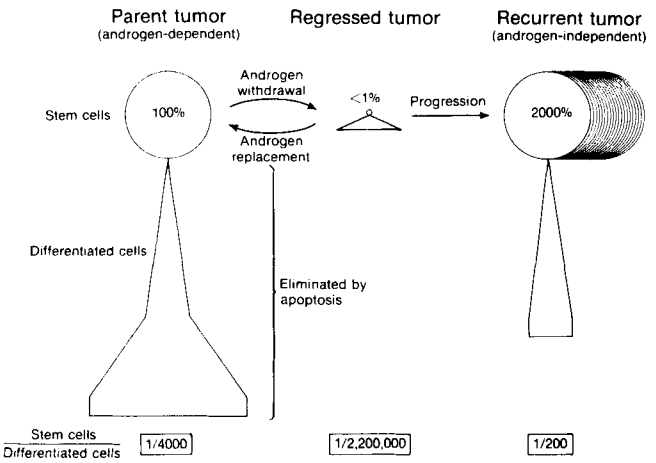

Figure 1. Model of stem cell composition of the androgen-dependent Shionogi carcinoma. The change in the ratio of stem cells/differentiated cells, which occurs after androgen withdrawal, is shown. The effect of androgen replacement in stimulating the differentiation of stem cells in the regressed tumor and the recovery of apoptotic potential also is illustrated. (Modified from Bruchovsky N, Rennie PS, Coldman AJ, Goldenberg SL, To M, Lawson D. Effects of androgen withdrawal on the stem cell composition of the Shionogi carcinoma. *Cancer Res* 1990; 50:2275–82.)

Furthermore, there is mounting evidence that progression is associated with the activation of previously androgen-repressed genes, resulting in the production of autocrine or paracrine growth factors that substitute for androgens in stimulating the division and differentiation of surviving parent stem cells.[6–8] This implies that progression begins early in the treatment history of the tumor coincident with the cessation of androgen-induced differentiation of stem cells in the parent tumor.[6] It follows that if androgens are replaced before progression begins, as explained by the hypothesis illustrated in Figure 1, the surviving stem cells should give rise to an androgen-dependent tumor which would be amenable to retreatment by androgen withdrawal. Androgen-induced differentiation of stem cells with recovery of apoptotic potential thus provides a rationale for intermittent androgen-withdrawal therapy of androgen-dependent tumors.

Despite possible applications to the long-term management of inoperable, incompletely excised, or locally recurrent prostate cancer, little information is available about this approach. In the past, estrogens occasionally were administered on a cyclic basis to men with advanced prostate cancer and in some, multiple clinical responses were observed.[9] An improved quality of life was achieved owing to reduced intake of estrogens, but little insight was gained into tumor-related biological effects of intermittent therapy owing to the limited availability of sensitive markers of tumor response and progression. More precise evaluation of these endpoints is now possible with sequential monitoring of the tumor marker, prostate-specific antigen (PSA).[10,11]

In the current study, we describe the effects of consecutive cycles of androgen withdrawal and replacement on the maintenance of apoptotic potential in the Shionogi carcinoma and also on the serum PSA levels measured at monthly intervals for up to 4 years in several men with prostate cancer treated with intermittent androgen withdrawal.

Materials and Methods

Shionogi Carcinoma

In preparation for transplant, the parent androgen-dependent Shionogi mouse mammary carcinoma was excised and minced in tissue culture medium as described before.[12] Fragments of tissue containing a total of approximately 5×10^6 tumor cells were injected subcutaneously into individual male mice of the DDS strain. The diameters of the tumor which developed in each animal were measured in millimeters with calipers. The formula (length $\times$ width^2)/2 = mass (mg) was used to estimate the mean weight of the tumor.[13] When the tumor reached a weight of about 3 g, the host animal was castrated through an abdominal incision. Methoxyflurane anesthesia was used for surgery. After the tumor had regressed to a weight of about 1 g, it was excised and minced yielding fragments of tissue which were implanted into a noncastrated male animal. This cycle of transplantation and castration was repeated several times with each of 16 originally separate tumors.

Prostate Cancer

Observations relevant to the proposed hypothesis have been made on a nonrandomized group of seven men, who having responded to initial androgen suppression, expressed an interest in regaining sexual potency. The mean age at initiation of treatment was 66 years (range, 56–77 years). Four patients had Stage C disease, three of whom had been treated previously by external-beam irradiation of the prostate; one patient had Stage D1 disease and two patients had Stage D2 disease. Informed consent was obtained from each patient.

The pretreatment evaluation included a full history and physical examination, and measurement of total serum testosterone, serum PSA by radioimmunoassay (Diagnostic Products Corporation, Los Angeles, CA), prostatic acid phosphatase by radioimmunoassay,[14] blood urea nitrogen, creatinine, alkaline phosphatase,

lactate dehydrogenase, and a complete blood count. Radiologic studies included radiographs of the chest, lumbar spine, and pelvis; a computerized tomography (CT) scan of the abdomen and pelvis to determine the extent of local disease and lymphadenopathy; and a transrectal sonogram of the prostate to measure glandular volume (assuming an elliptical shape[15]) and the size of any hypoechoic lesions within the gland. To complete the evaluation of metastatic disease, a bone scan was obtained.

Follow-up assessments were conducted at monthly intervals after the initiation of treatment. At each visit the serum testosterone and PSA were assayed again. The other biochemical tests, radiographs, CT scan, transrectal sonogram of the prostate, and bone scan generally were repeated every 4 to 6 months. During the initial part of this study, levels of serum PSA below 2 μg/l were not titrated; this was later altered so that the lower limit became 0.2 μg/l.

The treatment regimen used to produce an androgen-withdrawal effect was based on the sequential use of three agents as described before[16] and combined the following steps: (1) lead-in therapy with cyproterone acetate (100 mg/d) and diethylstilbestrol (0.1 mg/d) administered for 4 weeks (this reduces the serum testosterone into the castrate range and eliminates the possibility of a flare reaction occasionally induced by the administration of luteinizing hormone-releasing hormone [LHRH] agonist[17]); (2) goserelin acetate (3.6 mg) started after 4 weeks of lead-in therapy and given every 4 weeks thereafter; and (3) diethylstilbestrol stopped after 8 weeks with maintenance of cyproterone acetate to prevent hot flashes.[18] Administration of goserelin acetate and cyproterone acetate was continued until the serum PSA had decreased into and remained in the normal range for at least 4 months and there was no clinical evidence of disease progression. Treatment was resumed when the level of serum PSA recovered to about 20 μg/l, an upper limit that was set arbitrarily. The same steps then were followed to initiate the new cycle of therapy.

Results

Castration-Induced Progression of the Shionogi Carcinoma

To demonstrate the outcome of conventional ablative therapy on the Shionogi carcinoma, parent androgen-dependent tumor cells were transplanted into male animals, which were castrated 25 days later when the resultant tumor mass in each host attained an estimated weight of 3 g. As shown in Figure 2, the tumors regressed to a mean weight of 0.4 g 43 days after transplant and then began to increase in size; a mean weight of 3 g was achieved 75 days after transplant. When the recurrent tumor cells were harvested and transplanted at this time into a noncastrated male animal, the resultant tumor grew with the same doubling time as the parent tumor but did not respond to castration. These observations indicate that progression to an androgen-independent state was initiated by primary androgen suppression with an estimated time to androgen independence of 50 days.

Effects of Repeated Androgen Withdrawal and Replacement on the Shionogi Carcinoma

To determine whether the emergence of androgen independence could be delayed by intermittent exposure

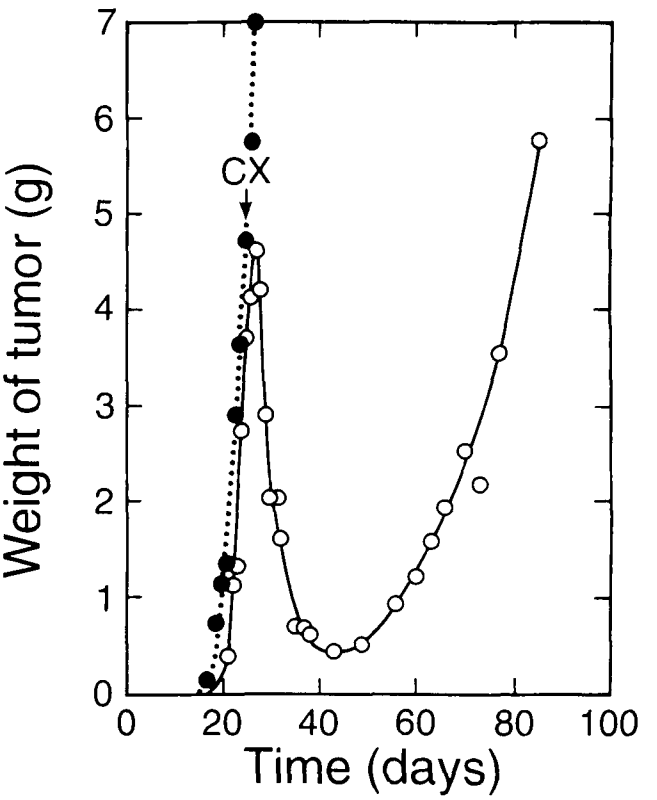

Figure 2. Effects of castration on progression of the Shionogi carcinoma. About 5 × 10^6 cells of the parent androgen-dependent Shionogi carcinoma were injected into a male DDS strain mouse. When the tumor reached a weight of 3 g, the host animal was castrated (CX). Recurrent growth was observed until the tumor attained a weight of about 3 g, at which time it was removed and transplanted (5 × 10^6 cells) into a noncastrated mouse. When the transplanted recurrent tumor reached a weight of 3 g, the animal was castrated (CX). Each point represents the mean weight of at least five tumors in separate mice. ○: parent androgen-dependent tumors; ●: recurrent androgen-independent tumors.

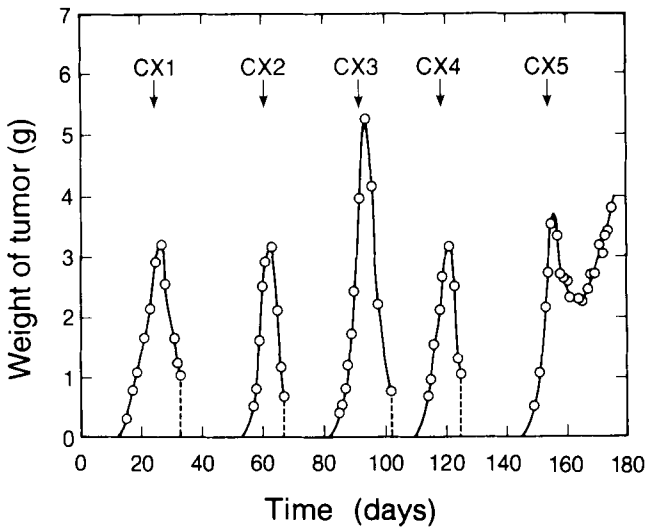

Figure 3. Effects of intermittent androgen withdrawal on Shionogi carcinoma. About 5 × 10^6 cells of the Shionogi carcinoma were injected into a male DDS strain mouse. When the tumor reached a weight of 3 g, the host animal was castrated (CX1–5). After the tumor had regressed to a weight of 1 g, it was implanted into a noncastrated male mouse. This cycle of transplantation and castration was repeated five times.

of the parent Shionogi carcinoma to androgens, the tumor was transplanted into a succession of male animals, each of which was castrated when the estimated tumor weight became about 3 g. The results of this experiment are shown in Figure 3.

After the initial implant, the parent Shionogi carcinoma became palpable after an interval of about 15 days and reached a weight of 3 g after another 10 days. After castration of the host animal (CX1), the tumor continued to grow for 1 to 2 days before the onset of apoptosis was evident. About 6 days after castration, the tumor regressed to 30% of its precastration weight. After transplant of this tumor into a second male host, the latent interval before development of the next tumor was slightly longer at 23 days. Castration (CX2) was again followed by involution of the tumor. Transplant of the regressed cells into a third male host resulted in the development of a palpable tumor after 18 days. A third castration (CX3) resulted in yet another regression of tumor cells. Transplant of the surviving tumor cells into a fourth host was followed by a short latent period of only 11 days before a tumor mass was palpable. The doubling time of 24 to 48 hours essentially was the same as that observed during previous growth periods. Regression of tumor was induced by castration (CX4), and after a latent period of 24 days, the transplanted regressed cells gave rise to a new tumor mass. Castration (CX5) brought about a partial 40% regression of the tumor after which autonomous growth abruptly supervened.

These results demonstrate that apoptotic potential can be reinduced in a tumor cell population at least five times by replacement and withdrawal of endogenous testosterone. A similar pattern of consecutive responses has been reproduced in 16 different tumors with a mean time to androgen independence of 150 days. In keeping with the hypothesis outlined in Figure 1, these experimental results imply that progression of the Shionogi carcinoma is averted when androgens are replaced early, i.e., 6 days after castration (Fig. 3) rather than after a lengthy delay of 50 days (Fig. 2).

Case Reports

Case 1

The patient was a 57-year-old man with local progression of previously irradiated, Stage C, moderately differentiated adenocarcinoma. During the observation period described in Figure 4, he underwent four courses of androgen-withdrawal therapy. Serum PSA was suppressed with each treatment (A) in synchrony with the suppression of serum testosterone. In contrast, the rise in PSA after interruption of treatment (B) lagged behind the recovery of testosterone affording no-treatment periods of 7, 7, and 6 months, respectively. The volumes of the prostate before and at the end of the fourth treatment estimated by ultrasonography were 25 ml and 11 ml, respectively. Such regression of prostate associated with a decline in

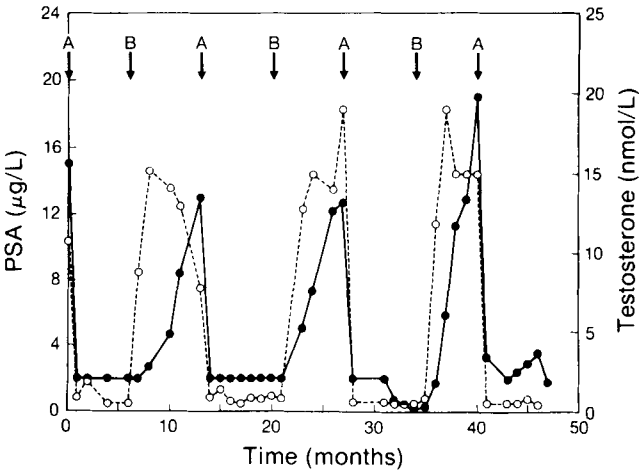

Figure 4. Effects of intermittent androgen withdrawal: Case 1. A 57-year-old man with local progression of previously irradiated, Stage C, moderately differentiated adenocarcinoma. Androgen withdrawal started at time A and interrupted at time B, yielding treatment intervals of 6, 7, 7, and 7 months and no-treatment intervals of 7, 7, and 6 months, respectively. ○: serum testosterone; ●: serum PSA.

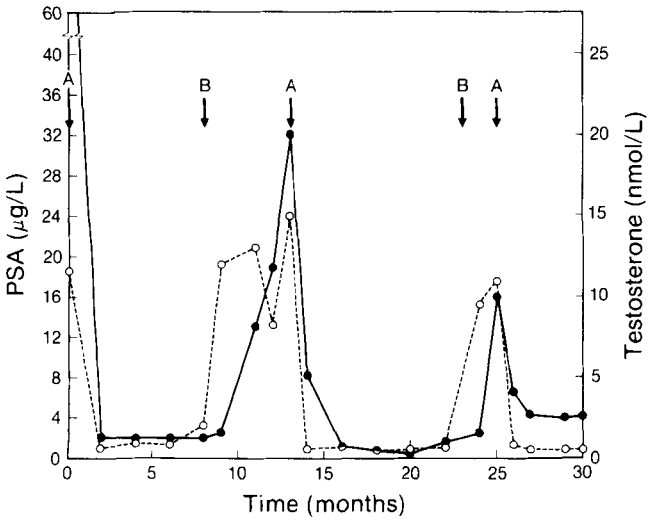

Figure 5. Effects of intermittent androgen withdrawal: Case 2. A 77-year-old man with local progression of previously irradiated, Stage C, moderately differentiated adenocarcinoma. Androgen withdrawal started at time A and interrupted at time B, yielding treatment intervals of 8, 10, and 5 months and no-treatment intervals of 5 and 2 months, respectively. O: serum testosterone; ●: serum PSA.

PSA suggests that the androgen-dependent (apoptotic) state of the tumor is maintained even after four cycles of treatment.

Case 2

This 77-year-old man presented with local progression of previously irradiated, Stage C, moderately differentiated adenocarcinoma. Androgen withdrawal was initiated three times with the results shown in Figure 5. Serum PSA was suppressed during each round of treatment (A) in synchrony with the suppression of testosterone. The rise in PSA after interruption of treatment (B) again lagged behind the recovery of testosterone. In this case, the length of the first no-treatment interval was 5 months and the second, 2 months.

Case 3

This 72-year-old man presented with local progression of previously irradiated, Stage C, well-differentiated adenocarcinoma. The results in Figure 6 show that serum PSA was suppressed with each (A) of three treatment cycles in parallel with the suppression of serum testosterone. Similarly, the rise in PSA after interruption of treatment (B) coincided with the recovery of testosterone. Thus, PSA production in this patient was more closely related to the concentration of testosterone than in Cases 1 and 2 in whom the level of serum PSA lagged behind the recovery of testosterone. As a result, the no-treatment period was short.

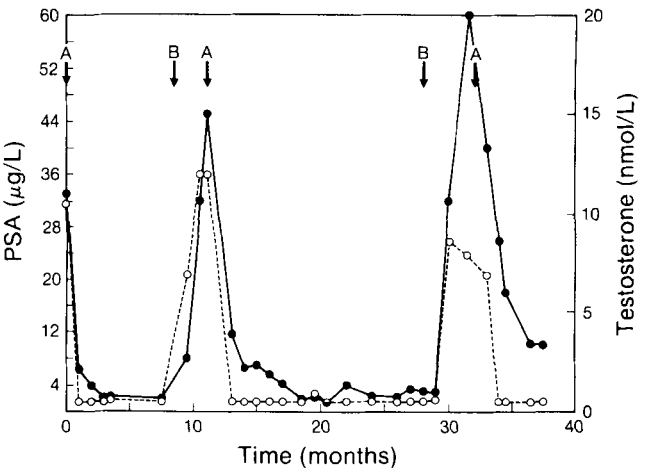

Figure 6. Effects of intermittent androgen withdrawal: Case 3. A 72-year-old man with local progression of previously irradiated, Stage C, well-differentiated adenocarcinoma. Androgen withdrawal started at time A and interrupted at time B, yielding treatment intervals of 8.5, 17, and 5.5 months and no-treatment intervals of 2.5 and 4 months, respectively. O: serum testosterone; ●: serum PSA.

Case 4

This 62-year-old man presented with Stage D1, poorly differentiated adenocarcinoma. Lymph node involvement with metastatic disease was confirmed at staging pelvic lymphadenectomy. The patient had no previous hormonal treatment. The results of three courses of androgen-withdrawal therapy are summarized in Figure 7. With each treatment (A), the sup-

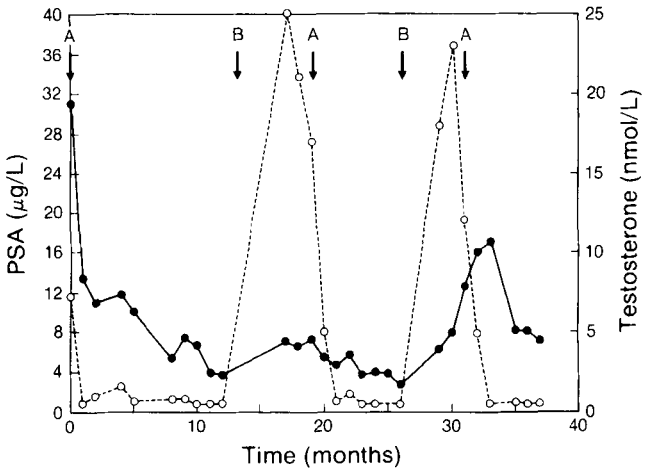

Figure 7. Effects of intermittent androgen withdrawal: Case 4. A 62-year-old man with Stage D1, poorly differentiated adenocarcinoma and no previous hormonal treatment. Androgen withdrawal started at time A and interrupted at time B, yielding treatment intervals of 13, 7, and 6 months and no-treatment intervals of 6 and 5 months, respectively. O: serum testosterone; ●: serum PSA.

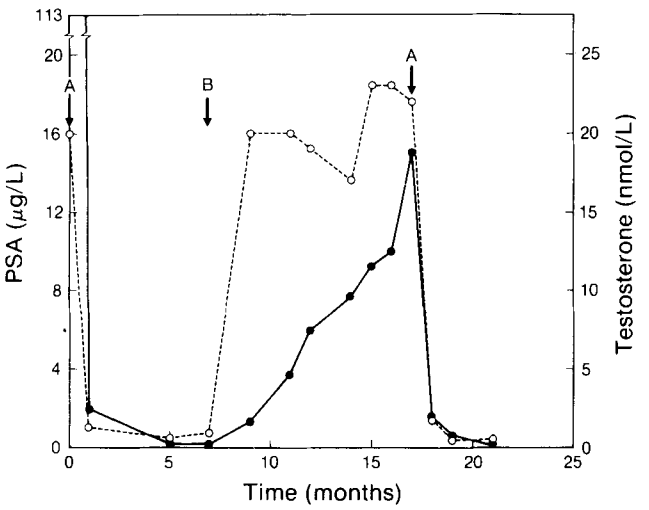

Figure 8. Effects of intermittent androgen withdrawal: Case 5. A 69-year-old man with Stage C, moderately differentiated adenocarcinoma and no previous treatment. Androgen withdrawal started at time A and interrupted at time B, yielding treatment intervals of 7 and 4 months, respectively, and a no-treatment interval of 10 months. O: serum testosterone: ●: serum PSA.

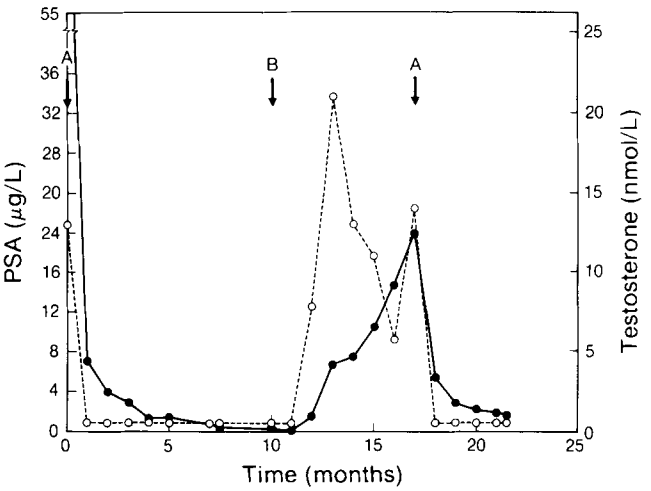

Figure 9. Effects of intermittent androgen withdrawal: Case 6. A 56-year-old man with Stage D2, moderately differentiated adenocarcinoma and no previous treatment. Androgen withdrawal started at time A and interrupted at time B, yielding treatment intervals of 10 and 4.5 months, respectively, and a no-treatment interval of 7 months. O: serum testosterone; ●: serum PSA.

pression of serum PSA lagged behind that of testosterone. The increase in PSA after the first interruption of treatment (B) was much slower than the rise after the second interruption. This implies that the androgen sensitivity of an individual tumor may change during the course of intermittent therapy.

Case 5

This man, 69 years of age, presented with a markedly elevated level of serum PSA attributed to Stage C, moderately differentiated adenocarcinoma. The patient had not been treated previously. Observations during two courses of androgen-withdrawal therapy are summarized in Figure 8. As in Cases 1 through 3, serum testosterone and PSA were suppressed in unison with each of the two treatments (A). However, in contrast to Case 3, the rise in PSA after interruption of treatment (B) was very slow, affording a long no-treatment period of 10 months.

Case 6

This 56-year-old man presented with Stage D2, moderately differentiated adenocarcinoma. Distant metastases were confined to lymph nodes. The patient had no previous treatment. The results of two courses of androgen-withdrawal therapy are presented in Figure 9. The patterns of suppression and recovery of serum testosterone and PSA resemble those observed in Case 5 with Stage C disease. During the first no-treatment period the volume of the prostate, estimated by ultrasonography, increased from 15 ml to 25 ml. This was reduced to 11 ml by the second period of androgen suppression that followed. Lymphadenopathy as assessed by CT scan had resolved during the latter treatment cycle at 20 months.

Case 7

At the time of presentation, this 67-year-old man had Stage D2, poorly differentiated adenocarcinoma metastatic to bone. The patient had no previous treatment. The patient underwent two courses of androgen withdrawal, the results of

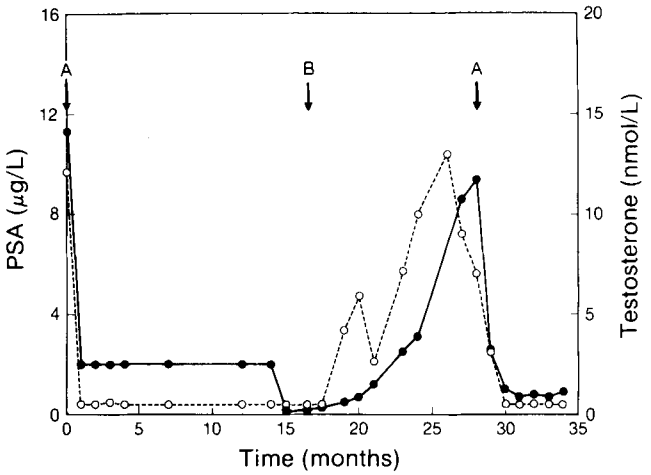

Figure 10. Effects of intermittent androgen withdrawal: Case 7. A 67-year-old man with Stage D2, poorly differentiated adenocarcinoma and no previous treatment. Androgen withdrawal started at time A and interrupted at time B, yielding treatment intervals of 17 and 6 months, respectively, and a no-treatment interval of 11 months. O: serum testosterone; ●: serum PSA.

which are summarized in Figure 10. After a lengthy initial treatment period of 17 months, the rates of recovery of serum testosterone and PSA were relatively slow, allowing for a long no-treatment period of 11 months.

Discussion

Although successive waves of apoptosis have been induced in the rat prostate with repeated cycles of testosterone withdrawal and replacement,[19] multiple regressions of an androgen-dependent tumor have seldom, if ever, been demonstrated. However, it is clear from our current observations (Fig. 3), that consecutive apoptotic regressions can be induced in the androgen-dependent Shionogi carcinoma. To circumvent the difficulty of titrating the concentration of exogenously administered testosterone, regressing tumor cell populations were transplanted from a castrated male host to an intact male animal. These cells generated populations that responded successively to androgen withdrawal with tumor atrophy. Tumor regression was unequivocal after each of the first four castrations, but only partial regression was observed after the fifth. This suggests that early progression of the Shionogi carcinoma can be averted by maintaining the androgen-dependent state of the tumor with endogenous androgen replacement. Indeed, intermittent androgen suppression (Fig. 3) resulted in an apparent three-fold longer time to androgen independence than monosuppression of androgens (Fig. 2), i.e., 150 versus 50 days.

The reversibility of new types of androgen-withdrawal therapy based on the use of anti-androgens and LHRH agonists makes it relatively easy to alternate a patient between periods on and off androgen withdrawal. Also, with sequential measurements of serum testosterone and PSA, successive periods of tumor response and regrowth can be monitored with considerable precision.

Assuming that serum PSA is related to volume of tumor,[20–23] the data presented in Figures 4 through 10 imply that the androgen-dependent apoptotic state of prostatic carcinoma also can be maintained by repeated androgen withdrawal and replacement. In the group of seven patients on whom observations were made, between two and four consecutive cycles of this form were administered over periods of 21 to 47 months without definite evidence of progression. The subsequent course of these patients, now about 2 years, has been unremarkable with no deaths and a suggestion of incipient independence of PSA regulation in three cases. In those patients in whom serial transrectal sonograms of the prostate were available for comparison, the volume of the prostate decreased by a mean 45% (n = 7) during regression and increased by a mean 66% (n = 5) during the recovery of serum testosterone to the normal range. With treatment, no obvious increase in size of prostatic hypoechoic lesions occurred. These tended to become smaller or ill-defined and more difficult to measure.

In every patient, serum PSA was suppressed with each sequential treatment in synchrony with the suppression of testosterone. In attempting to interpret the significance of fluctuations in this parameter, at least three factors must be considered: (1) the synthesis of PSA may be inhibited by androgen withdrawal without any associated apoptotic cell death; (2) the synthesis of PSA may continue unabated in the absence of androgen, but if a large number of cells is eliminated from the prostate cancer owing to apoptosis, the overall production of PSA would decline; and (3) reduction of PSA may reflect a combination of arrested synthesis and accelerated cell death. Our results favor the latter interpretation, owing to the biphasic response of PSA in Cases 3, 4, and 6 (Figs. 6, 7, and 9). In Case 6 (Fig. 9), for example, two sequential decreases of serum PSA induced by therapy were characterized by an initial sharp fall succeeded by a slower rate of decline. This pattern would be in keeping with a dual effect of androgen withdrawal on PSA, an immediate one on the synthesis of this tumor marker, and a second slower response reflecting gradual elimination of tumor cells.

The observed rate of increase of PSA after interruption of treatment was variable, suggesting a difference in the androgen sensitivity between tumors in different patients (Fig. 6 versus Fig. 8) and in the androgen sensitivity of the same tumor between different rounds of intermittent therapy (Fig. 7).

In patients in whom the PSA rose rapidly in parallel with the recovery of serum testosterone (Figs. 5 and 6), it is doubtful that recurrent tumor growth alone could account for this change. Rather, the sharp rise probably is explained by a direct effect of testosterone on the synthesis of PSA.[24] In patients in whom the rise in PSA lagged behind the recovery of serum testosterone (Figs. 4, 7–10), a greater likelihood exists of a correlation between the level of PSA and tumor volume.[23]

The duration of androgen withdrawal to achieve the maximum reduction of tumor volume likely exceeds the interval between the time that therapy is initiated and the point when serum PSA falls to 4 μg/l, the upper limit of the normal range. With further treatment, the concentration might continue to fall to the lower limit of detection (0.2 μg/l), as in Figure 8, implying continuation of the apoptotic process.

The time required for apoptotic potential to be restored in a testosterone-stimulated recurrent tumor is

unknown. Androgen suppression was resumed when the serum PSA recovered to an arbitrarily chosen limit of 20 μg/l. In the five men who underwent sonographic studies at this time, increases in prostatic volume were clearly observed; all subsequently responded to therapy showing a decrease in serum PSA. This suggests that apoptotic potential of tumor cells can be regained in association with a relatively small elevation of PSA.

Only those patients in whom serum PSA is normalized by initial androgen withdrawal should be considered as candidates for intermittent therapy. Consistent with the observations of Miller et al.,[25] our experience suggests that the prognosis is poor in patients in whom the PSA fails to decrease to a stable level within the normal range during the first 8 months of androgen suppression: a sign of early progression to androgen independence. The median survival in a group of eight such men with Stage D2 disease who were treated without interruption was 18 months compared with 40 months in a similar group of men whose PSA was normalized by treatment (unpublished data).

Whether intermittent androgen withdrawal and its effects on tumor progression alter survival in a beneficial or adverse way is unknown, although the possibility of an improved outcome has been considered by Klotz et al.[9] No unfavorable effects on survival have been suggested by our experience with such therapy. However, it would be of considerable interest to compare the results of intermittent versus continuous androgen suppression in patients in whom the PSA is lowered into the normal range by initial therapy.

Owing to the fact that the function of the testis and the concentration of serum testosterone return to normal slowly over a period of 8 to 14 weeks when the patient is off treatment, it is unlikely that acute symptoms and signs of tumor flare will be precipitated by intermittent androgen suppression. Under such conditions of deliberate and gradually increasing hormonal stimulation, a greater chance exists that the androgen-dependent (apoptotic) state of the tumor will be restored, thus setting the stage for another response to androgen deprivation. This is in contrast to the adverse effects of androgen priming on androgen-independent (Stage D3) prostate cancer. Sudden clinical deterioration may be observed owing to accelerated growth of tumor cells which remain androgen-sensitive but irreversibly nonregressing.[26,27]

More obvious advantages of intermittent androgen suppression include an improved quality of life with recovery of sexual function and apparent prolongation of the androgen-dependent state of the tumor. This treatment may, in addition, provide more favorable conditions for response to chemotherapy, applications to the management of disease in earlier stages, and reduced cost of treatment.

References

1. Bruchovsky N, Lesser B, Van Doorn E, Craven S. Hormonal effects on cell proliferation in rat prostate. *Vitamin Horm* 1975; 33:61–102.
2. Kyprianou N, Isaacs JT. Quantal relationship between prostatic dihydrotestosterone and prostatic cell content: critical threshold concept. *Prostate* 1987; 11:41–50.
3. Bruchovsky N, Brown EM, Coppin CM, Goldenberg SL, Le Riche JC, Murray NC, et al. The endocrinology and treatment of prostate tumor progression. In: Coffey DS, Bruchovsky N, Gardner WA Jr, Resnick MI, Karr JP, eds. Current concepts and approaches to the study of prostate cancer: progress in clinical and biological research. New York: Alan R Liss, 1987:348–87.
4. Schulze H, Oesterling JE, Isaacs JT, Coffey DS. Hormonal therapy of prostate cancer: limitations in the total androgen ablation concept. In: Coffey DS, Resnick MI, Dorr FA, Karr JP, eds. A multidisciplinary analysis of controversies in the management of prostate cancer. New York: Plenum Press, 1988:215–24.
5. Krieg M, Tunn S. Pathological aspects of the malignant and benign growth of the human prostate. In: Aumuller G, Krieg M, Senge T, eds. New aspects in the regulation of prostatic function. Munich: W Zuckschwerdt Verlag, 1989:3–12.
6. Bruchovsky N, Rennie PS, Coldman AJ, Goldenberg SL, To M, Lawson D. Effects of androgen withdrawal on the stem cell composition of the Shionogi carcinoma. *Cancer Res* 1990; 50:2275–82.
7. Furuya Y, Sato N, Akakura K, Ichikawa T, Suzuki N, Sato R, et al. Paracrine growth stimulation of androgen-responsive Shionogi carcinoma 115 by its autonomous subline (Chiba subline 2). *Cancer Res* 1990; 50:4979–83.
8. Rennie PS, Bruchovsky N, Coldman AJ. Loss of androgen dependence is associated with an increase in tumorigenic stem cells and resistance to cell-death genes. *J Steroid Biochem Mol Biol* 1990; 37:843–47.
9. Klotz LH, Herr HW, Morse MJ, Whitmore WF Jr. Intermittent endocrine therapy for advanced prostate cancer. *Cancer* 1986; 58:2546–50.
10. Ercole CJ, Lange PH, Mathisen M, Chiou RK, Reddy PK, Vessella RL. Prostatic specific antigen and prostatic acid phosphatase in the monitoring and staging of patients with prostatic cancer. *J Urol* 1987; 138:1181–84.
11. Oesterling JE. Prostate specific antigen: a critical assessment of the most useful tumor marker for adenocarcinoma of the prostate. *J Urol* 1991; 145:907–23.
12. Bruchovsky N. The metabolism of testosterone and dihydrotestosterone in an androgen-independent tumour: a possible correlation between dihydrotestosterone and tumour growth in vivo. *Biochem J* 1972; 127:561–75.
13. Simpson-Herren L, Lloyd HH. Kinetic parameters and growth curves for experimental tumor systems. *Cancer Chemother Rep* 1970; 54:143–74.
14. Goldenberg SL, Silver HKB, Sullivan LD, Morse MJ, Archibald EL. A critical evaluation of a specific radioimmunoassay for prostatic acid phosphatase. *Cancer* 1982; 50:1847–51.
15. Terris MK, Stamey TA. Determination of prostate volume by transrectal ultrasound. *J Urol* 1991; 145:984–87.
16. Bruchovsky N, Goldenberg SL, Rennie PS, Coppin CM. Presuppression of the pituitary: an adjunct to LHRH agonist ther-

apy of prostatic cancer [abstract]. *Clin Invest Med* 1989; 12:R-478.

17. Vallis K, Waxman J. Tumour flare in hormonal therapy. In: Stoll BA, ed. Endocrine management of cancer: II. Contemporary therapy. Basel: S Karger AG, 1988:144–52.
18. Goldenberg SL, Bruchovsky N. Use of cyproterone acetate in prostate cancer. *Urol Clin North Am* 1991; 18:111–22.
19. Sandford NL, Searle JW, Kerr JFR. Successive waves of apoptosis in the rat prostate after repeated withdrawal of testosterone stimulation. *Pathology* 1984; 16:406–10.
20. Stamey TA, Kabalin JN, McNeal JE, Johnstone IM, Freiha F, Redwine EA, et al. Prostate specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate: II. Radical prostatectomy treated patients. *J Urol* 1989; 141:1076–83.
21. Partin AW, Carter HB, Chan DW, Epstein JI, Oesterling JE, Rock RC, et al. Prostate specific antigen in the staging of localized prostate cancer: influence of tumor differentiation, tumor volume and benign hyperplasia. *J Urol* 1990; 143:747–52.
22. Gleave ME, Hsieh J-T, Wu H-C, von Eschenbach AC, Chung LWK. Serum prostate specific antigen levels in mice bearing human prostate LNCaP tumors are determined by tumor volume and endocrine and growth factors. *Cancer Res* 1992; 52:1598–1605.
23. Tunn UW, Goldschmidt AJW. Effects of temporary antiandrogenic treatment prior to radical prostatectomy. In: Murphy G, Khoury S, Chatelain C, Denis L, eds. Recent advances in urological cancers: diagnosis and treatment. Paris: American Cancer Society/EORTC, 1990:102–7.
24. Young CY-F, Montgomery BT, Andrews PE, Qiu S, Bilhartz DL, Tindall DJ. Hormonal regulation of prostate-specific antigen messenger RNA in human prostatic adenocarcinoma cell line LNCaP. *Cancer Res* 1991; 51:3748–52.
25. Miller JI, Ahmann FR, Drach GW, Emerson SS, Bottaccini MR. The clinical usefulness of serum prostate specific antigen after hormonal therapy of metastatic prostate cancer. *J Urol* 1992; 147:956–61.
26. Fowler JE Jr, Whitmore WF Jr. Considerations for the use of testosterone with systemic chemotherapy in prostatic cancer. *Cancer* 1982; 49:1373–7.
27. Bruchovsky N. Androgens and antiandrogens. In: Holland JF, Frei E, Bast RC Jr, Kufe DW, Morton DL, Weichselbaum RR, eds. Cancer Medicine. 3rd ed. Philadelphia, London: Lea & Febiger, 1992 (in press).