Prostate-Specific Antigen Response to Withdrawal of Megestrol Acetate in a Patient With Hormone-Refractory Prostate Cancer
[Case Report]

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Abstract

Clinically significant responses after withdrawal of flutamide in patients with hormone-refractory prostate cancer (HRPC) are well documented. Failure to recognize this syndrome of response results in potential morbidity due to salyage therapy, confusion in interpretation of disease state, and introduction of a possible source of error in clinical trials. In this case report, we describe a patient with HRPC whose prostate-specific antigen levels decreased substantially in response to withdrawal of megestrol acetate. Such a response should be considered when megestrol acetate is used in the treatment of HRPC.


HRPC = hormone-refractory prostate cancer; MA = megestrol acetate; PSA = prostate-specific antigen

Prostate cancer is the most common malignant disease in men in North America; an estimated 317,000 new cases and 41,400 deaths occurred in 1996. [1] During the course of their disease, 70% of patients will have metastases. [2] Hormonal therapies with orchiectomy, diethylstilbestrol, flutamide, or leuprolide acetate are the first-line treatments of metastatic disease, and associated response rates are approximately 80%. In most patients, however, the disease progresses in 12 to 18 months, and overall survival is 24 to 30 months. Progression of disease during primary hormonal treatment indicates hormone-refractory prostate cancer (HRPC). In this setting, chemotherapy and second-line hormonal therapies have resulted in modest response rates with no survival advantage. Withdrawal of hormonal agents may result in similar response rates.

Megestrol acetate (MA) has been shown to be effective therapy for metastatic prostate cancer. This synthetic progestin blocks androgen receptors and lowers the serum androgen levels through inhibition of release of luteinizing hormone and 5 alpha-reductase. [3,4] As first-line therapy, response rates have ranged from 18 to 75%. [5,6] The drug has also been shown to have modest but reproducible efficacy as secondline treatment of HRPC. [7,8]

Response to withdrawal of antiandrogenic agents is clinically significant and well documented in patients with HRPC. [9-12] Scher and Kelly [10] reported a decrease in prostate-specific antigen (PSA) levels of more than 50% after withdrawal of flutamide in 57% of 35 patients with HRPC. The responses lasted for a median of 5 months. In another study, [12] these investigators described nine more cases of
response to withdrawal of flutamide; four patients had an objective partial response. Under similar clinical conditions, Sartor and associates [13] reported a 78% decrease in PSA levels in 16 of 36 patients after withdrawal of flutamide when aminoglutethimide was initiated concurrently. More recently, responses after withdrawal of bicalutamide (Casodex) were observed in 29% of patients. [11] After withdrawal of flutamide, a response is noted within days, but the response to withdrawal of bicalutamide may not be noted for up to several weeks, presumably because of its longer half-life. Response to withdrawal of MA has been previously described in a single case report. [14] Herein we describe a second case of response of PSA levels after discontinuation of use of MA.

REPORT OF CASE

In January 1993, stage IV prostate cancer was diagnosed in a 62-year-old man in whom an increased PSA level was found during routine screening. A needle biopsy revealed an adenocarcinoma (Gleason sum, 9), and a bone scan showed disease metastatic to the hips, vertebrae, and ribs. He was initially treated with leuprolide, but 8 months later disease progression was noted by an increasing PSA level and new lesions on a bone scan. In September 1993, as part of a clinical trial to treat HRPC, the patient received MA (160 mg four times a day) and continued hormone suppression with leuprolide (Figure 1). With this therapeutic regimen, findings on a bone scan remained stable, and the PSA level decreased from 69 to a nadir of 31 ng/mL (a more than 50% decrease). In June 1994, the PSA level began a slow increasing trend, which later accelerated. In October 1994, the PSA level increased to a maximum of 370 ng/mL, and a bone scan showed new sites of activity in the calvaria, sacrum, ribs, and vertebrae. The patient had no symptoms, and use of MA was discontinued. The PSA level then spontaneously decreased at monthly intervals from 370 to 136 to 45 and subsequently to 2 ng/mL. Vinblastine sulfate and estramustine phosphate were initiated just before the value of 2 ng/mL was measured; thus, the duration of response cannot be assessed beyond 3 months. Findings on a bone scan remained stable.
DISCUSSION

We present a syndrome of response of PSA levels to withdrawal of MA in a patient with HRPC. In this patient, whose tumor had once been responsive to MA therapy, PSA levels decreased from 370 ng/mL to normal after discontinuation of use of MA. The decrease was rapid and sustained. These observations are important because they substantiate a previous report of MA withdrawal syndrome by Dawson and McLeod [14] and imply that the syndrome is not limited to withdrawal of antiandrogens (bicalutamide or flutamide).

The mechanism of response to withdrawal of hormone therapy remains to be elucidated, but in vitro data suggest that genetic instability of the androgen receptor may have a critical role. Mutations in the androgen receptor gene are rarely detected in hormone-responsive prostate cancer, but Taplin and coworkers [15] noted point mutations in 5 of 10 tumors from patients with HRPC. Furthermore, functional studies of these mutant androgen receptors demonstrate the potential for receptor activation by the nonandrogens progesterone and estrogen. Thus, receptor mutation, a dynamic process, has the capacity to yield altered ligand binding and aberrant stimulatory activity, [16,17] which may provide a selective growth advantage. Withdrawal of this stimulatory signal may explain the withdrawal response noted in our patient, which is analogous to the induction of apoptosis caused by androgen blockade in testosterone-dependent tumor cells. [18]

The MA withdrawal syndrome described in the current case was similar to that in the previously...
reported case. In both patients, the duration of MA therapy was lengthy (13 months and 24 months, respectively), and the time frame of withdrawal responses was durable (greater than 3 months and 5 months, respectively). In addition, the decrease in PSA levels was noted shortly after discontinuation of the drug, consistent with the short half-life of MA. The most interesting similarity was the substantial decrease of the PSA level after withdrawal of MA. In both cases, the lowest recorded PSA level after withdrawal of MA was less than the measured level before treatment with MA. This finding raises the possibility that withdrawal of MA may trigger a cytotoxic event for tumor cells, which affects both MA-dependent and independent populations. This latter effect could possibly occur through interference of paracrine growth factors from the MA-dependent cells, loss of structural-vascular integrity of the tumor, creation of a toxic environment in the presence of necrosis, or a nonspecific augmentation of immune function.

**CONCLUSION**

The syndrome of PSA response to withdrawal of MA is an important scientific observation because it suggests that agents other than the antiandrogens have the capacity to change function from antagonist to agonist in HRPC. This syndrome is of equal clinical importance because failure to recognize it may result in administration of unnecessary therapy, may deprive the patient of "positive news" regarding a temporary arrest in progression of disease, and may cloud interpretation of subsequent clinical therapy including clinical trials. Further evaluation is needed to document the incidence, clinical significance, and duration of this withdrawal effect.

**REFERENCES**

12. Kelly WK, Scher HI. Prostate specific antigen decline after antiandrogen withdrawal: the flutamide withdrawal syndrome. J


