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Antiandrogen Withdrawal Syndrome Associated with Prostate Cancer Therapies

Incidence and Clinical Significance

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Abstract

The antiandrogen withdrawal syndrome is a well established phenomenon in prostate cancer. It is widely accepted that a subset of patients will benefit from the withdrawal of antiandrogen or steroidal hormone from hormonal therapy, exhibiting decreasing prostate-specific antigen (PSA) values and clinical improvement. The pathophysiology of antiandrogen withdrawal syndrome is not completely understood, although androgen receptor gene mutations seem to be the likely explanation. Currently, it is not possible to identify the subset of patients whose tumours will respond to antiandrogen or steroid withdrawal. Tumours that will respond may be classified as androgen-independent and hormone-sensitive tumours as opposed to androgen-independent and hormone-insensitive tumours that do not respond. Patients who respond to antiandrogen withdrawal experience approximately 6 months with improved quality of life; however, it is unknown if this translates into prolonged survival. At the very least, antiandrogen withdrawal offers a therapeutic modality that is not associated with adverse effects and improves quality of life even if only for a very limited time.

Recent reports suggest that adding a secondary hormonal therapy such as amino-

glutethimide, ketoconazole or steroidal hormones may enhance the response rate and prolong response time to the antiandrogen withdrawal syndrome. However, unless there is proof that this secondary hormonal manipulation prolongs survival, maintenance of quality of life is mandatory because of the possible adverse effects from these potent drugs.

The fact that about 30% of patients will respond to antiandrogen or steroid withdrawal in hormone refractory prostate cancer must be taken into account in clinical trials of new cytotoxic agents which have been and will be conducted. Cessation of flutamide for at least 4 weeks and, in the case of bicalutamide, even 8 weeks, is mandatory before antiandrogen withdrawal syndrome can be excluded as the cause of decreasing PSA values.

The antiandrogen withdrawal syndrome offers another piece of the puzzle of prostatic carcinoma, but at the same time it demonstrates how different advanced prostate cancer cells may react to therapeutic strategies and, therefore, hormone refractory prostate cancer remains a difficult challenge which must be solved in the future.

Hormonal therapy and antiandrogens are widely used for the treatment of prostate cancer.[1] Several therapeutic strategies, such as antiandrogen monotherapy or total androgen blockade using a gonadotropin releasing hormone (GnRH) agonist or bilateral orchiectomy in combination with an antiandrogen, are used in the noncurative treatment of prostate cancer.

Hormonal therapy of prostate cancer was first described by Huggins and Hodges in 1941.[2] First results at that time suggested that hormonal therapy might be curative, but it turned out that after an initial response in approximately 80% of patients with prostate cancer to hormonal therapy, about 40% of patients will develop tumour progression within 3 years of therapy. 50% of these patients will die within 12 months.[3-5] Treatment of hormone-resistant prostate cancer is a great challenge for urologists and medical oncologists because currently there is no therapy available which has been shown to prolong survival in these patients.

Prostate specific antigen (PSA), since its isolation and description in seminal fluid by Wang and et al.,[6] is the most clinically useful tumour marker for monitoring response to therapy.[7] The first apparent sign of tumour progression under therapy is increasing PSA values. Clinical progression of prostate cancer will follow rising PSA values in most of patients who receive treatment. On the other hand, it is widely accepted that declining PSA values under therapy are a surrogate marker of tumour response to therapy. The widespread use of PSA determinations for monitoring prostate cancer disease status lead to the discovery of a new syndrome – the antiandrogen withdrawal syndrome.

New reports of secondary hormonal manipulation demonstrated decreasing PSA values after withdrawal of the antiandrogen in a significant subset of patients with hormone refractory disease. This observation, which will be discussed, is called 'antiandrogen withdrawal syndrome'.

1. Definition

'Antiandrogen withdrawal syndrome' is defined as a subjective and/or objective improvement following discontinuation of the antiandrogen in patients with rising PSA values under hormonal therapy, which includes the administration of an antiandrogen (also called maximum androgen blockade).

One of the first reports of antiandrogen withdrawal symptom was published by Kelly and Scher.[8] They treated 4 patients with hormone-resistant prostate cancer who were receiving combined androgen blockade with the nonsteroidal antiandrogen flutamide. All 4 patients showed a decrease in their PSA values, as well as subjective response after discontinuation of flutamide. At that time this observation was called 'flutamide withdrawal syndrome'. Fur-

ther reports demonstrated a similar effect after discontinuation of the nonsteroidal antiandrogens bicalutamide[9,10] and nilutamide,[11] as well as steroidal antiandrogens such as cyproterone acetate,[12,13] estrogens such as diethylstilbesterol[14] and progestational agents, i.e. megestrol[15] (see table I). Therefore, flutamide withdrawal syndrome was renamed 'antiandrogen withdrawal syndrome' or even more recently 'steroid hormone withdrawal syndrome'.[18] Although the term 'steroid withdrawal syndrome' is the more recent synonym it should be noted that this phenomenon is observed more often with nonsteroidal antiandrogens and for this subgroup of drugs it is preferable to use the term 'antiandrogen withdrawal syndrome'.

Table I. Reports of antiandrogen/steroid hormone withdrawal syndrome

Reference	Year	Agent
Kelly et al.[8]	1993	Flutamide
Collinson et al.[16]	1993	Flutamide
Small et al.[9]	1994	Bicalutamide
Nieh et al.[10]	1995	Bicalutamide
Barthelemy et al.[17]	1996	Nilutamide
Huan et al.[11]	1997	Nilutamide
Sella et al.[12]	1998	Cyproterone acetate
Akakura et al.[13]	1998	Chlomadinone acetate
Bissada et al.[14]	1995	Diethylstilbesterol
Dawson et al.[15]	1995	Megestrol

2. Pathophysiology

The first evidence of the molecular basis of the antiandrogen withdrawal syndrome was demonstrated by Wilding et al.[19] in 1989. They proved that flutamide *in vitro* had a paradoxical growth stimulatory effect on the prostate cancer cell line LNCaP. In addition, flutamide was unable to inhibit the stimulatory effect of dihydrotestosterone in this hormone-sensitive prostate cancer cell line. In 1990, a mutation in the ligand binding domain of the androgen receptor in the LNCaP cell line was identified as the reason for the growth stimulatory effect of flutamide.[20] This mutation is not responsible for the observed growth stimulation of bicalutamide or nilutamide, but since then several other mutations have been discovered, not only in prostate cancer cell lines but also in tumour specimens.[21-23]

The cornerstone to understanding hormone resistance and learning how to overcome hormonal resistance in prostate cancer seems to be the androgen receptor (AR). This receptor belongs to the steroid receptor superfamily and is a potent intracellular signal transducer. The AR regulates prostatic growth and function. The AR gene is located on the X-chromosome and is comprised of 3 domains: the steroid binding domain at the C terminus; the central DNA binding domain; and the transactivation domain at the N terminus. The presence of AR protein as shown by immunohistochemistry does not correlate with response to treatment and disease outcome.[24] Also, the AR protein can still be detected in hormone refractory prostatic cancer.[25] Therefore, changes in AR receptor function may be involved in the differing responses of patients to hormonal therapy by modulating the signalling pathway starting from the ligand binding affinity of androgens up to the activation of the transcription factor functions of the AR. One of the first observations of altered AR function was the description of the point mutation of codon 877 in the AR gene in the cell line LNCaP by Veldschole et al.[20] This point mutations leads to an exchange of threonine to alanine. This exchange of a single amino acid leads to stimulation of the AR receptor by flutamide but not by bicalutamide or nilutamide. Transfection studies of the mutated AR gene demonstrate increased AR signalling activity explaining growth stimulatory effects in LNCaP cells by flutamide.[20] Since then several mutations of the AR gene in prostate cancer have been reported.[26] Mostly point mutations have been found and interestingly most mutations are located in the ligand binding domain. Suzuki et al.[27] were the first to report the codon 877 mutation in relation to the antiandrogen withdrawal syndrome. The LNCaP mutation of codon 877 was found in several patients, whereas all other reported mutations were detected only once. The human AR gene mutation database is available on the internet[28] and lists all reports of AR gene mutations currently detected.

This database shows the increasing number entries for prostate cancer (currently 60), as well as the LNCaP mutation. The results of mutation analysis show that point mutations may be a possible explanation for the androgen withdrawal syndrome. However, there is no single mutation responsible in all patients, and there is a significant subset of patients demonstrating androgen withdrawal syndrome but only a minor subset of patients with point mutations of the AR receptor.

Therefore, an alternative aetiology could be the amplification of the AR gene. In support of this idea, Visakorpi et al.[29] demonstrated that although no amplification was found in primary prostate cancer, up to 30% of investigated samples revealed AR gene amplification in hormone-resistant prostate cancer.

There is evidence from molecular biology analyses as to how the antiandrogen withdrawal syndrome can be explained, but currently, the data available do not sufficiently explain this syndrome in all patients.

3. Results of Antiandrogen Withdrawal in Hormone-Resistant Prostate Cancer

Androgen-independent prostate cancer develops under androgen ablation therapy. The median time to hormone resistance is usually 2 to 3 years.[30] An increasing PSA value under endocrine therapy is the first sign of hormone refractory prostate cancer (HRPC). In this situation Scher et al.[31] proposed a classification of 2 distinct different types of HRPC. First, androgen-independent and hormone-sensitive tumours. These tumours proliferate despite castrate levels of androgens. As a result of secondary hormonal manipulations these tumours will undergo apoptosis (programmed cell death), demonstrating their hormone-sensitive stage. The second type of HRPC is called hormone-independent, or androgen-independent and hormone-insensitive tumours. These tumours due not respond to secondary hormone manipulation or progress after second-line hormonal therapy. As the antiandrogen withdrawal syndrome belongs to the secondary hormonal therapies, it is obvious that not all patients will improve after cessation of antiandrogen therapy because a subset of patients will belong to the hormone-independent group. But a significant subset of patients, who belong to the androgen-independent but hormone-sensitive group, will experience falling PSA values after discontinuation of antiandrogen therapy.

3.1 Rate of Response Following Antiandrogen Withdrawal

Response to antiandrogen withdrawal syndrome is arbitrarily defined as a decrease in PSA values of more than 50% of the initial PSA values. Using this definition, a response to antiandrogen withdrawal has been seen in 17 to 80% of patients in published series (see table II). Most of the data available relate to the withdrawal of flutamide, but recent reports demonstrate a similar response rate for bicalutamide and other antiandrogens (table II). All reports emphasise that a decline in PSA values of more than 50% can be observed in a significant number of treated patients. This response correlates with clinical response. In addition, about 30% of patients will experience a partial response (PSA decline > 50%) and there is also a significant subset of patients with stable disease. In our own experience up to 20% of patients demonstrate stable PSA values[34] suggesting stable disease. Dupont et al.[38] reported that 26 out of 80 patients had stable disease according to the response criteria of the US National Prostate Cancer Project.

3.2 Time to Response Following Antiandrogen Withdrawal

An important point to assess the effect of antiandrogen withdrawal syndrome is the time to response. Therefore, patients with increasing PSA values after discontinuation of the antiandrogen can be treated with alternative therapies if they have not shown a biochemical response within the expected time frame.

After cessation of flutamide falling PSA values occur within 4 to 6 weeks or earlier after discontinuation.[18] If bicalutamide was used as antiandrogen the time to response seems to be prolonged

Table II. Summary of results of hormone withdrawal syndrome

Reference	Antiandrogen	No. of patients	No. of patients responding (%)[a]	Duration of response (months)	Additional treatment
Scher et al.[32]	Flutamide	57	16 (28)	4	None
Herrada et al.[33]	Flutamide	11	11 (28)	3.3	None
Breul and Paul[34]	Flutamide	12	2 (17)	6	None
Figg et al.[35]	Flutamide	21	7 (33)	3.7	None
Schellhammer et al.[36]	Flutamide	8	4 (50)	-	None
Hornak et al.[37]	Flutamide	35	8 (23)	4.1	None
Dupont et al.[38]	Flutamide	40	32 (80)	14.5	Aminoglutethimide and hydrocortisone
Sartor et al.[39]	Flutamide	29	14 (48)	8	Aminoglutethimide and hydrocortisone
Figg et al.[40]	Flutamide	17	11 (65)	11	Aminoglutethimide and hydrocortisone
Small et al.[41]	Flutamide	20	11 (55)	8.5	Ketoconazole and hydrocortisone
Schellhammer et al.[36]	Bicalutamide	14	4 (29)	-	None
Nieh[10]	Bicalutamide	3	1 (33)	6	None
Small and Srinivas[42]	Bicalutamide	1	1		None
Sella et al.[12]	Cyproterone	12	4 (33)	6	None

a >50% decline in prostate-specific antigen levels.

compared with flutamide because of the longer half-life of bicalutamide. An average of 4 to 8 weeks is needed before declining PSA values are noted.[36]

Because only case reports exist of other antiandrogens and steroidal hormones the expected time to response can not be determined, but the published data suggest that an effect can be expected within 2 months after discontinuation.

On the other hand, if no decline in PSA value is noted after 8 weeks following antiandrogen withdrawal and in that time 2 consecutive increasing PSA values were obtained, these patients are hormone-independent and can be treated by alternative treatment modalities, i.e. chemotherapy.

3.3 Duration of Response to Antiandrogen Withdrawal

Response to the antiandrogen withdrawal syndrome is of limited duration. Patients who demonstrate falling PSA values seem to benefit from simple discontinuation of the antiandrogen for about 3.3[33] to 14.5 months[38] for flutamide treated patients and for about 6 months[10] for bicalutamide treated patients (table II). Keeping in mind that currently there is no alternative therapy which prolongs survival in patients with hormone-resistant prostate cancer, a therapy option that is devoid of adverse effects and that offers patients 6 months of life with improved quality of life, seems to be a significant advantage for patients with prostate cancer. A very important factor in the improved quality of life is the psychological advantage for patients of the declining PSA values. Since PSA was introduced as a parameter to control for disease status, the quality of life in patients with prostate cancer depends significantly on the rate of decline of in PSA values. Even clinically asymptomatic patients demonstrate impaired quality of life if their PSA values are increasing.

3.4 Survival Following Antiandrogen Withdrawal

The question is, will antiandrogen withdrawal syndrome translate into prolonged survival in these patients? Mean survival in patients with hormone-resistant prostate cancer is about 12 months, therefore, prolonged survival, even if it will be only a few months, seems to be a significant gain for these

patients. Small and Srinivas[42] demonstrated a nonsignificant increase in total survival time from starting hormonal therapy for responders to antiandrogen withdrawal of 44.5 months compared with 35 months for nonresponders. Comparing survival time after initiation of the antiandrogen withdrawal syndrome they noted 13 months for responders and 12 months for nonresponders. Whether responders and nonresponders to the antiandrogen withdrawal show identical survival times needs to be proven in further studies, which are ongoing. The study of Small and Srinivas[42] suggests that patients who respond to antiandrogen withdrawal belong to a group of patients with a better prognosis, but this fact does not translate into prolonged survival after tumours become androgen-resistant but hormone-sensitive.

3.5 Defining Prognostic Criteria of Response to Antiandrogen Withdrawal

Because only a subset of patients will benefit from antiandrogen withdrawal it would be helpful to be able to stratify patients with hormone refractory cancer in order to establish prognostic parameters to identify patients who will respond to antiandrogen withdrawal, as well as nonresponders who could receive alternative therapy earlier on. There have been several attempts to identify which type of hormonal therapy may predict response to antiandrogen withdrawal. Scher et al.[32] and Herrada et al.[33] suggest that patients who have low androgen levels (following orchiectomy or GnRH agonist therapy) combined with an antiandrogen are more likely to respond than patients who received antiandrogen monotherapy. Contrary to the results obtained by Small and Srinivias,[42] Sartor et al.[39] could not find a difference in the response rate with regard to which type of hormonal therapy was used.

Several other parameters have been investigated, such as PSA value, alkaline phosphatase level, haemoglobin level, lactate dehydrogenase level, hepatic transaminase levels, histological grade, extent of bone disease, soft tissue extent, age and performance status. None of these parameters was found commonly to correlate with the response rate to antiandrogen withdrawal in these studies.[17,39,43] Furuya et al.[43] defined a subgroup of patients who experienced normalisation of their PSA values within 3 months after the start of initial hormonal therapy who showed a higher response rate to the antiandrogen withdrawal. Several groups[32,35,39,42] have shown that the duration of antiandrogen exposure is related to response after discontinuation of the antiandrogen. It seems that patients who respond to hormonal therapy quickly and over a prolonged period represent the subgroup of patients with hormone-sensitive tumours, who will benefit from secondary hormonal manipulation. On the other hand patients whose PSA values do not normalise within 3 months and experience early rising PSA values probably will not respond well to secondary hormonal therapy strategies.

4. Impact of Secondary Hormone Treatment Strategies on the Antiandrogen Withdrawal Syndrome

Knowing that a subset of patients may be classified as having androgen-independent but hormone-sensitive tumours, these patients may benefit not only from cessation of the antiandrogen but also from secondary hormonal manipulation. Secondary hormonal therapy is not a well described treatment modality. Some authors use this term to describe simple antiandrogen or steroid withdrawal, while others use this term to describe second-line antiandrogen treatment or inhibition of adrenal steroidogenesis and treatment with alternative steroids, i.e. glucocorticoids or progestins. Here we will focus on the use of inhibition of adrenal steroidogenesis and treatment with alternative steroids in addition to the withdrawal of the first line antiandrogen to produce maximum androgen blockade.

Several trials have been conducted using different treatment modalities (table II).

Blockade of adrenal androgen production to reduce peripheral testosterone has been investigated by several authors.[38,39] Aminoglutethimide induces a functional adrenalectomy by blocking several steps of hydroxylation in the steroid biosynthesis. Because this drug is not selective for sex-hormones, replacement of the glucocorticoids is necessary to

prevent adrenal insufficiency in patients treated with this agent. Figg et al.[40] demonstrated that in the 65% of patients who responded, the mean duration of response was 11 months. Sartor et al.[39] found a mean duration of response of 8 months in the 48% of treated patients who responded. Dupont[38] reported an 80% response rate in patients treated with aminogluthetimide and hydrocortisone and the mean duration of response after antiandrogen withdrawal was 14.5 months. These results are improved in terms of the rate of response as well as the duration of response compared with antiandrogen withdrawal alone.

An agent which is also used in this context is ketoconazole, which is widely used as antifungal drug. Ketoconazole blocks the cytochrome P450 enzyme system and therefore also acts as a potent inhibitor of adrenal and testicular androgen production. In hormone refractory prostate cancer ketoconazole produced a response rate of 62.5%, but a mean response duration time of only 3.5 months if it was administered when tumour progression was noted after the antiandrogen was withdrawn.[44] By combining antiandrogen withdrawal with ketoconazole and hydrocortisone the duration of response was prolonged to 8.5 months.[41] Newer agents for adrenal inhibition are under investigation, such as liarozole,[45] but to date no studies combining liarozole with antiandrogen withdrawal have been conducted.

Glucocorticoids were used for a long time as palliative treatment in prostate cancer.[46] Dawson et al.[46] treated patients with hydrocortisone (30 mg/day) together with flutamide withdrawal and demonstrated a response rate of 29%. Figg et al.[47] presented a case report in 1997 of a patient with PSA progression under maximum androgen blockade who received hydrocortisone and simultaneous antiandrogen withdrawal. This patient's PSA value dropped from 64 μg/L to below the level of detection. Especially remarkable in this particular case is the fact that this complete response was noted over 46 months. In a large cohort of 230 patients who were randomised to receive placebo plus hydrocortisone (40 mg/day) versus suramin plus hydrocortisone, overall 16% of patients responded with a greater than 50% decline in PSA values.[48]

Besides hydrocortisone other corticosteroids have been studied. Nishiyma and Terunuma[49] treated patients following progression after antiandrogen withdrawal with dexamethasone starting with 1.5 mg/day initially, decreasing it to 0.5 mg/day later on. Of the 7 treated patients, 4 patients (57%) experienced a decrease in PSA value of over 90% and a response duration of 3 to 11 months. This confirms a previous study of Storlie et al.,[50] in which they reported a response rate of 61% for PSA value decline and 79% for symptomatic improvement in a total of 38 patients treated with dexamethasone (1.5 mg/day).

It remains open to question as to whether patients with hormone refractory prostate cancer may benefit from secondary hormonal therapy at the time of antiandrogen withdrawal, although treatment with aminoglutethimide is especially intriguing. Since there is no proof that the decline of PSA values at that stage of the disease is associated with prolonged survival it is mandatory to look for quality of life in these patients. Particularly the adverse effects of any drugs used must be taken into account.

5. Impact of the Antiandrogen Withdrawal Syndrome on Study Protocol of Clinical Trials in Hormone Refractory Prostate Cancer

Before the first reports of antiandrogen withdrawal syndrome appeared in 1993 it was unknown that in a subset of approximately 30% of patients discontinuation of antiandrogen would result in decreasing PSA values. In particular, phase II treatment trials investigating new cytotoxic drugs must be looked at if patients may have responded because of antiandrogen withdrawal rather than because of the investigated substance.[51] Since the antiandrogen withdrawal syndrome became known and widely accepted, patients entering clinical trials have to discontinue the antiandrogen before entry into a study (at least 4 weeks before for flutamide and 8 weeks before for bicalutamide). Also at

least 2 consecutive rising PSA values should be obtained before patients can be included in clinical trials to control for the effect of antiandrogen hormone withdrawal syndrome.

6. Antiandrogen Withdrawal or Discontinuation of Complete Hormonal Therapy

The antiandrogen withdrawal syndrome should not lead to discontinuation of GnRH agonist therapy. It is known that prostate cancer always remains sensitive to androgens. In HRPC, both androgen-independent/hormone-sensitive tumours and hormone-independent tumours will proliferate under endogenous or exogenous testosterone.[45] Discontinuation of GnRH agonists will result in decreased survival, even if in the group with continued hormonal therapy the prolongation of life was only of short duration as reported from the Eastern Cooperative Oncology Group.[52] Adding exogenous testosterone was found to result in progressive disease in 87% of treated patients with increased risk of serious complications such as cord compression, pain progression or death.[53] These results were also reported by Manni et al.,[54] including increased toxicity, worse outcome and failing to demonstrate androgen priming prior to chemotherapy. Although a suppressed castrate level of testosterone may persist for up to 1 year after GnRH agonist treatment for more than 2 years, persistence is very variable and not predictable.[55]

These results seem to be controversial in the literature because of a review of a total of 205 patients of the Southwest Oncology Group. 32 patients in this study discontinued hormonal therapy and no survival benefit was seen in either group.[56] But in this study, overall survival in both groups was very short with a median value of only 6 months, suggesting that the patient population had far advanced disease, in whom a survival difference would be difficult to detect.

The existing data indicate that most prostatic carcinoma in the hormone refractory stage would show increased progression in the presence of androgens. Therefore, continued gonadal androgen suppression should be considered standard care for patients with hormone-independent prostatic cancer.[45]

7. Conclusion

The antiandrogen withdrawal syndrome offers another piece in the puzzle of prostatic carcinoma, in that we are able to understand how the prostate cancer cell is able to escape hormonal therapy, but at the same time, it demonstrates how different advanced prostate cancer cells may react to therapeutic strategies. The antiandrogen withdrawal syndrome is not a simple solution for hormone refractory prostate cancer. Therefore, hormone refractory prostate cancer will remain a difficult challenge that has to be solved in the future.

References

1. Crawford ED, DeAntonio EP, Labrie F, et al. Endocrine therapy of prostate cancer: optimal form and appropriate timing. J Clin Endocrin and Metab 1995; 80: 1062-6
2. Huggins C, Hodges CV. Studies on prostatic cancer, effect of castration of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Res 1941; 1: 293-7
3. Schulze H, Isaacs JT, Senge T. Inability of complete androgen blockade to increase survival of patients with advanced prostate cancer as compared to standard hormonal therapy. J Urol 1987; 137: 909-11
4. Sogani PC, Fair WR. Treatment of advanced prostatic cancer. Urol Clin North Am 1987; 14: 353-71
5. Crawford ED, Eisenberger MA, McLeod DG, et al. A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. N Engl J Med 1989; 321: 419-24
6. Wang MC, Valenzuela IA, Murphy GP, et al. Purification of a human prostate specific antigen. Invest Urol 1979; 17: 159-63
7. 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
8. Kelly WK, Scher HI. Prostate-specific antigen decline after antiandrogen withdrawal. J Urol 1993; 149: 607-9
9. Small EJ, Carroll PR. Prostate-specific antigen decline after casodex withdrawal: evidence for an antiandrogen withdrawal syndrome. Urology 1994; 43: 408-10
10. Nieh PT. Withdrawal phenomenon with the antiandrogen casodex. J Urol 1995; 153: 1070-2
11. Huan SD, Gerridzen, RG, You J, et al. Antiandrogen withdrawal syndrome with nilutamide. Urology 1997; 49: 632-4
12. Sella A, Flex D, Sulkes A, et al. Antiandrogen withdrawal syndrome with cyproterone acetate. Urology 1998; 52: 1091-3
13. Akakura K, Akimoto S, Furuya Y, et al. Incidence and characteristics of antiandrogen withdrawal syndrome in prostate cancer after treatment with chlormadinone acetate. Eur Urol 1998; 33: 567-71
14. Bissada NK, Kaczmarek AT. Complete remission of hormone refractory adenocarcinoma of the prostate in response to withdrawal of diethylstilbesterol. J Urol 1995; 153: 1944-5

15. Dawson NA, McLoed DG. Dramatic prostate specific antigen decrease in response to discontinuation of megestrol acetate in advanced prostate cancer: expansion of the antiandrogen withdrawal syndrome. J Urol 1995; 153: 1946-7
16. Collinson MP, Daniel F, Tyrrell CJ, et al. Response of carcinoma of the prostate to withdrawal of flutamide. Br J Urol 1994; 72: 662-3
17. Barthelemy Y, Colombel M, Gasman D, et al. Antiandrogen withdrawal syndrome in the hormonal treatment of metastatic prostatic cancer in hormonal escape. Prog Urol 1996; 6: 93-7
18. Kelly WK, Slovin S, Scher HI. Steroid Hormone withdrawal syndromes. Urol Clin North Am 1997; 24: 421-31
19. Wilding G, Cheng M, Gelman EP. Aberrant response in vitro of hormone responsive prostate cancer cells to antiandrogens. Prostate 1989; 14: 103-14
20. Veldscholte J, Ris-Stalpers C, Kuipers GG, et al. A mutation in the ligand binding domain of the androgen receptor of human LNCaP cells affect binding characteristics and response to anti-androgens. Biochem Biophys Res Common 1990; 173: 534-43
21. Culig Z, Hobisch A, Cronauer MV, et al. Mutant androgen receptor detected in an advanced stage prostatic carcinoma is activated by adrenal androgens and progesterone. Mol Endocrinol 1993; 7: 1541-50
22. Gaddipati GP, McLeod DG, Heidenberg HB, et al. Frequent detection of codon 877 mutation in the androgen receptor gene in advanced prostate cancer. Cancer Res 54: 2862-4
23. Newmark JR, Hardy EO, Tonb DC, et al. Androgen receptor gene mutations in human prostate cancer. Proc Nat Acad Sci USA 1992; 89: 6319-23
24. Sadi MV, Walsh PC, Barrack ER. Immunohistochemical study of androgen receptors in metastatic prostate cancer: Comparison of receptor content and response to hormonal therapy. Cancer 1991; 67: 3057-64
25. Kleinerman DI, Troncoso P, Pisters LL, et al. Expression and structure of the androgen receptor in bone metastases of hormone refractory prostate cancer. J Urol 1996; 155: 1254A
26. Klocker H, Culig Z, Hobisch A, et al. Androgen receptor mutations in prostate cancer. In: Wirth M, Altwein JE, Schmitz-Dräger B, et al., editors. Molecular biology of prostate cancer. Berlin: Walter de Gruyter, 1998: 81-8
27. Suzuki H, Akakura K, Komiya A, et al. Codon 877 mutation in the androgen receptor gene in advanced prostate cancer: relation to antiandrogen withdrawal syndrome. Prostate 1996; 29: 153-88
28. The androgen receptor gene mutations database. Available online at URL: http://www.mcgill.ca/androgendb/
29. Visakorpi T, Hyytinen E, Koivisto P, et al. In vivo amplification of the androgen receptor gene and progression of human prostate cancer. Nat Genet 1995; 9: 401-6
30. Newling DW, Dennis L, Vermeylen K. Orchiectomy versus goserelin and flutamide in the treatment of newly diagnosed metastatic prostate cancer. Cancer 1993; 72 (12 Suppl.): S3793-8
31. Scher HI, Steineck G, Kelly WK. Hormone-refractory ("D3") prostate cancer: refining the concept. Urology 1995; 46: 142-8
32. Scher HI, Zhang ZF, Cohen L, et al. Hormonally relapsed prostatic cancer: Lessons from the flutamide withdrawal syndrome. Adv Urol 1995; 8: 61-95
33. Herrada J, Dieringer P, Logothetis CJ. Characterization of patients with androgen-independent prostatic carcinoma whose serum prostate specific antigen decreased following flutamide withdrawal. J Urol 1996; 155: 620-3
34. Breul J, Paul R. Das "Antiandrogen-Entzugssyndrom". Erste klinische Erfahrung und Literaturübersicht. Akt Urol 1996; 27: 267-70
35. Figg WD, Sartor O, Cooper MR, et al. Prostate specific antigen decline following the discontinuation of flutamide in patients with stage D2 prostate cancer. Am J Med 1995; 98: 412-4
36. Schellhammer PF, Venner P, Haas GP, et al. Prostate specific antigen decreases after withdrawal of antiandrogen therapy with bicalutamide or flutamide in patients receiving combined androgen blockade. J Urol 1997; 157: 1731-5
37. Hornak M, Bardos A, Concalves F. The antiandrogen withdrawal syndrome: decrease in prostate specific antigen serum levels after withdrawal of antiandrogens. Rozhl Chir 1997; 76: 435-7
38. Dupont A, Gomez J, Cusan L, et al. Response to flutamide withdrawal in advanced prostate cancer in progression under combination therapy. J Urol 1993; 150: 908-13
39. Sartor O, Cooper M, Weinberger M, et al. Surprising activity of flutamide withdrawal, when combined with aminoglutethimide, in treatment of 'hormone-refractory' prostate cancer. J Natl Cancer Inst 1994; 86: 222-7
40. Figg WD, Dawson N, Middleman A, et al. Flutamide withdrawal and concomitant aminoglutethimide in patients with hormone refractory prostate cancer. Acta Oncologica 1996; 35: 763-5
41. Small EJ, Baron A, Bok R. Simultaneous antiandrogen withdrawal and treatment with ketoconazole and hydrocortisone in patients with advanced prostate carcinoma. Cancer 1997; 80: 1755-9
42. Small EJ, Srinivas S. The antiandrogen withdrawal syndrome: experience in a large cohort of unselected patients with advanced prostate cancer. Cancer 1995; 76: 1428-34
43. Furuya Y, Akimoto S, Akakura K, et al. Response of prostate-specific antigen after androgen withdrawal and prognosis in men with metastatic prostate cancer. Urol Int 1998; 60: 28-32
44. Small EJ, Baron AD, Fippin L, et al. Ketoconazole retains activity in advanced prostate cancer patients with progression despite flutamide withdrawal. J Urol 1997; 4: 1204-7
45. Reese DM, Small EJ. Secondary hormonal manipulations in hormone refractory prostate cancer. Urol Clin North Am 1999; 26: 311-21
46. Dawson N, Cooper MR, Figg WD, et al. Antitumor activity of suramin in hormone-refractory prostate cancer when hydrocortisone treatment and flutamide withdrawal are prospectively controlled for as potentially confounding variables. Cancer 1995; 76: 453-62
47. Figg WD, Kroog G, Duray P, et al. Flutamide withdrawal plus hydrocortisone resulted in clinical complete response in a patient with prostate carcinoma. Cancer 1997; 79: 1964-8
48. Small EJ, Marshall ME, Reyno L, et al. Superiority of suramin plus hydrocortisone (S+H) over placebo plus hydrocortisone (P+H): Results of a multicenter double-blind phase III study in patients with hormone refractory prostate cancer. Proc Am Soc Clin Oncol 1998; 17: 308-12
49. Nishiyma T, Terunuma M. Hormone/antihormone withdrawal and dexamethasone for hormone-refractory prostate cancer. Int J Urol 1998; 5: 44-7
50. Storlie JA, Buckner JC, Wiseman GA, et al. Prostate specific antigen levels and clinical response to low dose dexamethasone for hormone-refractory metastatic prostate carcinoma. Cancer 1995; 76: 96-100

51. Scher IH, Kelly WK. Flutamide withdrawal syndrome: its impact on clinical trials in hormone-refractory prostate cancer. J Clin Oncol 1993; 11: 1566-72
52. Taylor CD, Elson P, Trump DL. Importance of continued testicular suppression in hormone-refractory prostate cancer. J Clin Oncol 1993; 11: 2167-72
53. Fowler JE, Whitmore WF. Consideration for the use of testosterone with systemic chemotherapy for prostatic cancer. Cancer 1982; 49: 1373-7
54. Manni A, Bartholomew M, Caplan R, et al. Androgen priming and chemotherapy in advanced prostate cancer: evaluation of determinants of clinical outcome. J Clin Oncol 1988; 6: 1456-66
55. Hall MC, Fritzsch RJ, Sagalowsky AI, et al. Prospective determination of the hormonal response after cessation of luteinizing hormone-releasing hormone agonist treatment in patients with prostate cancer. Urology 1999; 53: 898-902
56. Hussain M, Wolf M, Marshall E, et al. Effects of continued androgen-deprived therapy and other prognostic factors on response and survival in phase II chemotherapy trials for hormone-refractory prostate cancer: a Southwest Oncology Group Report. J Clin Oncol 1994; 12: 1868-75

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