Cancer Chemother Pharmacol (2005) 56 (Suppl 1): s58–s63
DOI 10.1007/s00280-005-0100-x

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Hormone treatment for prostate cancer: current issues and future directions

Published online: 5 November 2005

Abstract Most prostate cancers are androgen-dependent and essentially respond to androgen ablation therapy. However, these tumors eventually become androgen-independent and progress despite androgen ablation. Since the androgen receptor (AR) sequence was determined, numerous studies have shown that AR plays a critical role in the development of androgen-refractory prostate cancer. Amplification of AR, mutations of AR, and deregulation of growth factors, cytokines and AR co-activators, which could be classified as AR-dependent pathways, are frequently observed in this condition. There are other pathways, AR-independent pathways that bypass AR, which involve neuroendocrine differentiation of prostate cancer cells, deregulation of apoptotic genes and unknown mechanisms related to down-regulation of AR. Androgen-refractory prostate cancers with the AR-dependent pathway could be treated by suppressing AR activity, whereas AR-independent tumors would require alternative management strategies. When more cell survival pathways are defined, improvement of patients' survival could be achieved by developing specific gene-targeting therapies that interfere with those pathways.

Keywords Prostate cancer · Androgen receptor · Androgen-ablation therapy · Androgen-refractory prostate cancer

This work was presented at the 20th Bristol-Myers Squibb Nagoya International Cancer Treatment Symposium, "New Concepts of Treatment Strategies for Hormone-Related Cancer", 11–12 March 2005, Nagoya, Japan.

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Introduction

Since the first observation by Huggins and Hodges in 1941, hormonal therapy has been the main option for advanced prostate cancer [14]. Most prostate cancers are androgen-dependent and essentially respond to androgen ablation therapy. However, these tumors eventually become androgen-independent and progress despite androgen ablation. At that juncture, the options are limited and most are palliative. Therefore, it is a major issue to clarify the mechanisms of development of androgen-refractory prostate cancer. Since the androgen receptor (AR) sequence was determined, numerous studies have been performed and shown that AR plays a critical role in the development of androgen-refractory prostate cancer [31, 36].

According to immunohistochemical analysis, most androgen-independent prostate cancers still express AR protein, suggesting that AR-dependent signaling is important for the development of androgen-refractory prostate cancer [21, 32]. Debes and Tindall [5] have divided the mechanisms of development of androgen-refractory prostate cancer into two pathways: those involving AR and those that bypass it. The former, AR-dependent pathways, include amplification or mutations of AR, deregulation of growth factors or cytokines and alteration of co-activators (Table 1). The latter, AR-independent pathways, include neuroendocrine differentiation of prostate cancer cells, deregulation of apoptotic genes and unknown mechanisms related to downregulation of AR. The present article focuses on these pathways and considers possible treatments of each pathway.

Mechanisms and possible treatments of androgen-refractory prostate cancer

AR-dependent pathway: amplification of AR

Visakorpi et al. [39] found high levels of AR amplification at the DNA and RNA level in 7 of 23 hormone-refractory

Table 1 Mechanisms of androgen-refractory prostate cancer and possible treatments

Mechanisms	Treatments
AR-dependent prostate cancer	
Amplification of AR	Complete androgen blockade
Mutation of AR	Development of antiandrogen
Deregulation of growth factors or cytokines	Dexamethasone (IL-6)
Alteration of co-activators	Gene-targeting therapy: antibody, RNAi
AR-independent prostate cancer	
Neuroendocrine differentiation of prostate cancer cells	Gene-targeting therapy: antibody, RNAi
Deregulation of apoptotic genes	Gene-targeting therapy: antibody, RNAi
Unknown mechanisms related to downregulation of AR	–

prostate cancer patients and in none of the specimens obtained from the same patients before therapy. However, almost all of the patients whose tumors overexpressed AR underwent androgen-deprivation monotherapy without administration of antiandrogens. Recently, Chen et al. [3] found that increase of AR mRNA is the only change consistently associated with the development of resistance to antiandrogen therapy. This increase of AR mRNA and protein was both necessary and sufficient to convert prostate cancer growth from the hormone-sensitive to the hormone-refractory stage, and was dependent on a functional ligand-binding domain. These researchers concluded that increased levels of AR confer resistance to antiandrogens by amplifying signal output from low levels of residual ligand and by altering the normal response to antagonists. Mizokami et al. [22] demonstrated that the adrenal androgen androstenediol maintains high concentrations in prostate cancer tissue even after androgen deprivation therapy. They also demonstrated that low concentrations of androstenediol induce more AR nuclear translocation than dihydrotestosterone in LNCaP cells and not PC-3 cells transfected with AR. These findings indicate that the loss of androgen sensitivity in these patients was caused by proliferation of cancer clones stimulated by the remaining androgen produced by adrenal glands, thus suggesting the importance of MAB therapy. Development of new antiandrogens that achieve complete androgen blockade could be effective for this mechanism.

AR-dependent pathway: mutations of AR

Androgen-refractory tumors may contain mutations in the AR gene. These mutations increase the number of ligands that can activate AR. AR gene mutation in prostate cancer cells was first identified in the LNCaP cell line, which was derived from a metastatic lesion of the lymph nodes of a patient with prostate cancer [38]. The AR gene of this cell line contains one mutation at codon 877 (Thr to Ala). Growth of LNCaP cells is stimulated in vitro by androgens, estrogens, progestogens and several antiandrogens, indicating a widely responsive property of the LNCaP cell. In clinical materials, Suzuki et al. [28] identified AR gene mutations, one of which was the same as LNCaP cells. Mutations in the AR gene have been detected in 10–20% of prostate cancer specimens. The gene frequency of mutation generally appears higher in hormone-refractory, metastatic tumors compared with untreated lower-grade primary tumors [8, 20, 28, 29, 33, 34]. Based on the mutations of AR in prostate cancer (which are published at http://www.mcgill.ca/androgendb/data.htm) the codon 877 mutation is the hot spot (Fig. 1). Several AR mutations have been isolated with increased frequency from prostate tumors and evaluated functionally in the laboratory. These AR mutants include Thr877Ser, Thr877Ala, His874Tyr, Val715Met, Leu701His + Thr877Ala and Tyr741Cys [4, 12, 19, 27, 33–35]. Some of them are summarized in Table 2 (see also Steketee et al. [27]). According to the three-dimensional structure of the AR ligand-binding domain, T877 directly interacts with the 17-hydroxyl group of androgens. All amino acid substitutions identified at position 877 have smaller side chains than the threonine in the wild-type receptor, indicating that increased space in the ligand-binding pocket is important in broadened ligand specificity [27]. As H874 does not directly interact with the ligand, its substitution by tyrosine is expected to change the ligand-binding pocket conformation indirectly [27]. Given that certain

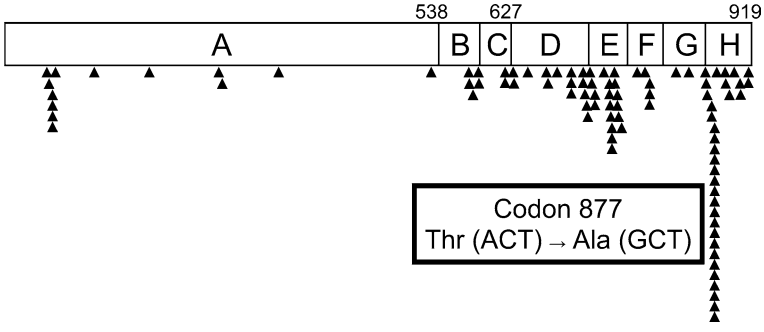

Fig. 1 Location of point mutation of androgen receptor identified in prostate cancer (http://www.mcgill.ca/androgendb/data.htm). Hot spot at codon 877 from Thr to Ala is observed

Table 2 Hyperactivated AR mutants in androgen-refractory prostate cancer (data from Steketee et al. [27])

Ligand	AR wild-type	AR (H874Y)	AR[a] (T877A)	AR (T877S)
Dihydrotestosterone	+ + +	+ + +	+ + +	+ + +
Dehydroepiandrosterone	–	+	+	+
Androstenedione	+ +	+ +	+ +	+ +
Progesterone	+	+ +	+ + +	+ + +
Cortisol	–	+	+	–
Estradiol	+	+ +	+ +	+ +
Antiandrogens				
Cyproterone acetate	+	+	+ + +	+ + +
Hydroxyflutamide	–	+	+ +	+
Bicalutamide	–	–	–	–

[a]Mutation identical to that found in LNCaP cell line

mutations can alter AR ligand specificity, AR mutation might play a key role in "antiandrogen withdrawal syndrome" [17, 29]. This phenomenon occurs in a subset of patients who experience a relapse of tumor growth, and is characterized by increasing serum prostate-specific antigen (PSA) concentration after long-term antiandrogen treatment. The cessation of antiandrogen medication improves symptoms and serum PSA levels decrease, suggesting that antiandrogen acts agonistically in the tumor cells to promote growth. Our previous study found that in two of four patients who experienced improvement following antiandrogen withdrawal (among a total of 22 total prostate cancer patients), AR mutations occurred during antiandrogen treatment [29]. These mutations were identical to that in LNCaP cells (T877A) and were undetected in untreated tumors. This finding together with the reports of others [2, 34] indicates that antiandrogen withdrawal syndrome is caused partly by AR "hyperactivated" mutation. Development of a new antiandrogen is clinically important for patients with androgen-refractory, but still hormone-responsive, prostate cancer.

AR-dependent pathway: deregulation of growth factors and cytokines

AR relies on alterations in growth factors such as insulin-like growth factor-I and cytokines such as interleukin (IL)-6, which activate AR. Ligand-independent activation of AR was first demonstrated in DU145 prostate cancer cells treated with growth factors such as epidermal growth factor, keratinocyte growth factor and insulin-like growth factor-I [4]. Sadar [26] has shown that the activator of protein kinase A pathway forskolin upregulates transcriptional activity of AR in a ligand-independent manner. Several clinical investigations have shown that serum levels of IL-6 are significantly elevated in patients with hormone-refractory disease [6, 23]. Ueda et al. [37] investigated the mechanism of cross-talk between the IL-6 and AR signal transduction pathways in LNCaP human prostate cancer cells. IL-6 induced several androgen-responsive element-driven reporters that are dependent on AR, increased phosphorylation of mitogen-activated protein kinase (MAPK) and activated the AR *N*-terminal domain (NTD). Immunoprecipitation and transactivation studies showed direct interaction between amino acids 234–558 of the AR NTD and STAT3 following IL-6 treatment of LNCaP cells. These results demonstrate that activation of human AR NTD by IL-6 is mediated through MAPK and STAT3 signal transduction pathways in LNCaP prostate cancer cells, and suggest that IL-6 is involved in androgen-independent progression of prostate cancer. Akakura et al. [1] investigated changes of serum IL-6 following dexamethasone therapy. Of 25 patients, 11 demonstrated ≥50% decline of serum PSA and 9 showed improvement of pain on dexamethasone therapy. Of eight patients who responded to dexamethasone therapy, five had ≥80% decrease of serum IL-6. In contrast, none of the eight non-responders showed remarkable IL-6 suppression. Response of PSA was not correlated to changes of serum dehydroepiandrosterone, dehydroepiandrosterone sulfate and androstendione. Significant suppression of serum IL-6 may be a mechanism for the effect of dexamethasone therapy in prostate cancer patients with progressive disease.

AR-dependent pathway: alteration of co-activators

Over the last several years, as our understanding of the basic mechanisms involved in AR signal transduction has increased, a search for alterations in AR co-regulatory molecules in prostate cancer has begun. Yeh and Chang [41] have cloned ARA70 as a specific co-regulator for AR. They also demonstrated that ARA70 functions as a transcriptional activator in DU145, an AR-negative prostate cancer cell line, in the presence of androgen. Gregory et al. [10] investigated expression of AR and three nuclear receptor co-activators, transcriptional intermediary factor (TIF)-2, steroid receptor co-activator (SRC)-1 and nuclear receptor co-activator amplified in breast cancer 1, in patients with prostate cancer. They demonstrated that levels of TIF-2 and SRC-1 rose with increases of AR expression in androgen-refractory disease. SRC-1 interacts directly with AR NTD via a conserved glutamine rich region between residues 1053 and 1123 and enhances IL-6-induced ligand-independent activation of AR NTD via an MAPK-dependent pathway in LNCaP human prostate cancer cells. A mechanism additional to MAPK

phosphorylation of SRC-1 may be required for ligand-independent activation of AR [37]. These results suggest that interactions between AR and co-activators represent another therapeutic target of treatment for androgen-refractory prostate cancer.

AR-independent pathway: neuroendocrine differentiation of prostate cancer cells

Androgen-refractory prostate cancer cells may also use survival pathways that completely bypass AR [11]. One important pathway is related to the neuroendocrine differentiation of prostate cancer cells. Neuroendocrine cells are more prevalent in androgen-refractory prostate cancer than in androgen-dependent disease. These cells secrete neuropeptides, which can increase proliferation of neighboring cancer cells, thereby allowing progression of androgen-refractory prostate cancer. Isshiki et al. [15] examined the significance of chromogranin A levels as serum marker for prostate cancer, and showed that poorly differentiated adenocarcinoma is associated with higher chromogranin A than well-differentiated disease ($P = 0.044$). Of the stage D cases with median PSA $\leq$ 172.1 ng/ml, those with higher chromogranin A had poorer prognosis than those with lower chromogranin A. Kamiya et al. [16] examined the relationship of neuron-specific enolase (NSE) to clinicopathological parameters to clarify the role of NSE in prostate cancer progression. They showed that serum NSE in metastatic prostate cancer patients was significantly higher than in patients without metastases. In metastatic patients who underwent endocrine therapy, the higher NSE group had significantly poorer cause-specific survival. Further studies are needed to evaluate the clinical implication of these neuropeptides.

AR-independent pathway: deregulation of apoptotic genes

Another important AR-independent pathway involves the deregulation of apoptotic genes such as the tumor-suppressor gene *PTEN* (phosphatase and tensin homolog) and the antiapoptotic gene *Bcl-2* [40]. The frequency of PTEN inactivation appears to increase during progression of prostate cancer [30]. PTEN protein has both lipid phosphatase and protein phosphatase activity and regulates cell cycle progression and apoptosis through reducing intracellular phosphatidylinositol 3,4,5-triphosphate level and the downstream Akt. Akt activates and upregulates pro-apoptotic proteins [42]. Loss of PTEN function may facilitate activation of AR signaling and progression to androgen-independence in prostate cancer [25]. One of the primary targets of Akt when it is blocking apoptosis is Bcl-2 [13]. Activated Akt frees Bcl-2 (which is bound to a protein called Bad), allowing it to increase cell survival. Overexpression of Bcl-2 has been shown to be associated with progression from androgen-sensitive to androgen-refractory metastatic phenotype of prostate cancer in both humans and animals [7, 18]. Recent studies have shown that Bcl-2 is a good target for single or combination therapy. Gleave et al. [9] demonstrated that antisense Bcl-2 oligodeoxynucleotides dramatically reduced tumor volume of LNCaP when compared with control mice.

AR-independent pathway: unknown mechanisms related to down-regulation of AR

Nakayama et al. [24] have shown that in vitro DNA methylation of the AR promoter in CpG islands is associated with loss of AR expression in human prostate cancer cells and tissues. AR was more frequently hypermethylated in hormone-refractory prostate cancer tissues (29%) compared with untreated primary tissues (10%). These results suggest that hypermethylation of the AR promoter region downregulates AR expression. However, the relationship between downregulation of AR expression and development of androgen-refractory prostate cancer is still unknown. Further studies are required to clarify the significance of downregulation of AR.

Conclusions

The mechanisms of androgen-refractory prostate cancer can be divided into two groups: AR-dependent and AR-independent pathways. The former might be managed by suppressing AR activity, whereas the latter will require new treatment strategies. Although many molecular studies of prostate cancer have been performed, the mechanisms by which prostate cancer cells survive after androgen-ablation therapy are still not totally understood. When more cell-survival pathways are defined, improvement of survival for patients might be achieved by developing specific gene-targeting therapies to interfere with those pathways.

Acknowledgements This paper is supported in part by Grants-in-Aid for scientific research from the Ministry of Education, Science, Technology and Culture, Japan (14207061, 16591582 and 16689026), the Japanese Urological Association (2000), the Ministry of Health, Labour and Welfare, Japan (Aid for Cancer Research), and Public Trust Haraguchi Memorial Cancer Research Fund (2003).

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