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Chapter 9

Reconsideration of Hormonal Therapy in the Era of Next-Generation Hormonal Therapy

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Additional information is available at the end of the chapter

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Abstract

Hormonal therapy is a major and effective tool in the treatment of prostate cancer patients. This is especially true for patients in the advanced stages of disease. Unfortunately, almost all prostate cancer cells will develop into castration-resistant prostate cancer (CRPC) despite continued therapy and suppression of testosterone levels. Up until 5–6 years ago, there was little effective therapy for the treatment of CRPC patients. However, recently, a variety of methodologies and drugs such as cabazitaxel and sipuleucel-T have been approved globally for the treatment of CRPC. Two novel drugs, abiraterone acetate and enzartamide, have also become available as potential treatment options. However, the anticancer effects of these two drugs are not always satisfactory in terms of prolonging survival. These drugs are also associated with adverse events and are expensive when compared with the costs of previously used anticancer drugs. In this section, we pay particular attention to hormonal therapies that do not include the use of abiraterone acetate or enzartamide. We believe that a detailed understanding of the range of currently available hormonal therapies, including their associated benefits and limitations, is important for supporting the prolongation of survival in patients with advanced prostate cancer. Therefore, this section offers a valuable discussion on the treatment strategies for prostate cancer including CRPC.

Keywords: steroidal antiandrogens, nonsteroidal anti-androgens, estrogens, steroids, castration-resistant prostate cancer

1. Introduction

Prostate cancer is one of the most common malignancies diagnosed worldwide in men. At present, prostate cancer patients with organ-confined disease can obtain an excellent oncological outcome through radical operation and radiotherapy. On the other hand, a variety of hormonal therapies are often necessitated for patients with advanced prostate cancer. Because the malignant aggressiveness of prostate cancer has been known to be suppressed by orchiectomy since the 1940s, androgen deprivation therapy (ADT) has been commonly administered. This is associated with the fact that the prostate is an androgen-dependent organ and that androgen receptor (AR) signaling plays an important role in the growth and progression of prostate cancer cells. In fact, as a first-line therapy, surgical castration, chemical castration, and anti-androgen treatment are usually used in the treatment of patients with metastatic prostate cancer [1]. Anti-androgens are broadly divided into two chemical types, steroidal and nonsteroidal. As a part of hormone therapy, estrogen and estrogen-containing agents can also be administered to patients with prostate cancer. A variety of glucocorticoids is also commonly used.

However, most hormone-naive prostate cancer patients will develop castration-resistant prostate cancer (CRPC) despite therapeutic suppression of testosterone levels and even though continued therapy can proceed without adverse effects. Furthermore, CRPC has a high malignant potential and aggressiveness. This is due to the number of heterogeneous types of cancer cells that develop a variety of abnormal signal pathways as a means to survive in the castration environment. In fact, the prognosis of patients with CRPC is often poor and no therapy that had high efficacy and high compliance had been available until the middle of the 2000s. In 2004, two clinical trials with large study populations and sophisticated methodologies demonstrated that the anticancer effects of docetaxel-based chemotherapy are superior to those of mitoxantrone and prednisolone treatments [2, 3]. Based on these facts, docetaxel has become a standard therapy for the treatment of CRPC. However, prolongation of survival by docetaxel chemotherapy is less than six months [4]. Additionally, docetaxel has major problems related to multiple and severe adverse events [3, 5]. Consequently, many urologists, physicians, and investigators have focused on the development of new therapeutic strategies to prolong survival in CRPC patients.

During the past 5–6 years, a variety of treatment methods and drugs for CRPC have been approved in many countries. Approved drugs include cabazitaxel and sipuleucel-T [6, 7]. In addition, ADT options for patients with CRPC have also changed during the past few years as the novel drugs, abiraterone acetate and enzartamide (termed as next-generation anti-androgens) have become available [8, 9]. Abiraterone is a specific steroidogenic inhibitor that irreversibly inhibits CYP17A1 [10]. Enzalutamide is an anti-androgen-receptor inhibitor that has been shown to improve prognosis in patients with CRPC [11]. Thus, many urologists and medical oncologists agree that treatment strategies for patients with CRPC are developing remarkably well [12]. However, the anticancer effects, including prolongation of patient survival, associated with these new treatments are not always adequate. For example, CRPC

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develops resistance to these second-generation agents quickly and thus the anticancer effects of abiraterone acetate and enzartamide can be decreased [13, 14].

Thus, although a variety of new anticancer agents have been developed, their anticancer effects in CRPC patients are not always satisfactory, particularly in terms of prolonging patient survival. In addition, CRPC patients often have many comorbidities due to past treatments and aging. Therefore, in discussions on treatment strategies for prostate cancer patients, it is essential to assess information regarding drug adverse reactions and safety. In addition, special attention must be paid to the cost of therapies as treatment periods are usually lengthy, and recently developed anticancer agents, including next-generation anti-androgens, are expensive. Based on these facts, we present in this chapter, the clinical benefits, safety, and caution points of hormonal therapies that do not involve next-generation antiandrogens. In other words, we will re-evaluate hormonal therapy for treatment of prostate cancer patients in the era of next-generation antiandrogen agents.

2. Antiandrogen agents

As mentioned earlier, prostate cancer cells are, in the majority of cases, androgen-dependent. Testosterone, of testicular origin, comprises 95% of androgen content. Androgens stimulate cell proliferation and tumor growth by binding to AR in the cancer cells. Therefore, the first-line of treatment for advanced prostate cancer has been androgen deprivation by medical castration through administration of luteinizing hormone-releasing hormone agonist/antagonists or by surgical castration with bilateral orchiectomy. Antiandrogens are AR receptor antagonists that compete with dihydroteststerone for AR binding. Upon binding, the antiandrogens act to inhibit the tumor growth in patients with prostate cancer. This section reviews first-generation antiandrogens used in the treatment of prostate cancer including CRPC.

2.1. Steroidal antiandrogens

Antiandrogens can be classified based on their chemical structure into two types, steroidal and nonsteroidal. The steroidal antiandrogens, cyproterone acetate, spironolactone, synthetic progestins, and chlormadinone acetate are well known in oncology. We first discuss the steroidal antiandrogens, progesterone analogue mifepristone (RU-486), cyproterone acetate, and the mineralocorticoid analogue, spironolactone. However, it should be noted that these agents are rarely used in clinical situations because of their partial androgenic agonistic–antagonistic activity.

RU-486 is a progesterone analogue best known as a progesterone receptor (PR) antagonist. It was developed in France as a medical approach to terminating pregnancy [15]. RU-486 also inhibits glucocorticoid receptor (GR) function and has been used for treating Cushing syndrome [16]. More importantly, RU-486 is also an AR antagonist. Binding studies indicate that it has a higher affinity for AR than either hydroxyflutamide or bicalutamide [17]. However, a Phase II study of RU-486 demonstrated limited activity in patients with CRPC. In that study,

RU-486 also stimulated a marked increase in the levels of adrenal androgens, testosterone, and dihydrotestosterone (DHT) [18].

Cyproterone acetate is nonspecific and can activate the mineralocorticoid receptor (MR), GR, and PR. A meta-analysis of randomized trials showed that combined androgen blockade (CAB) with nonsteroidal antiandrogens, including nilutamide and flutamide, appeared slightly favorable to cancer patient survival when compared with the effects of androgen suppression (AS) monotherapy. On the other hand, CAB with cyproterone acetate was associated with an inferior survival rate [19].

Spironolactone is an MR antagonist that is used to treat side effects related to mineralocorticoid excess. Richards et al. [20] showed that spironolactone significantly activates both wild type and mutant AR and that it should be avoided in the treatment of all patients with CRPC. As a result, CAB with steroidal antiandrogens has been recognized as an inferior treatment to the use of nonsteroidal antiandrogens and is considered unsuitable for prostate cancer treatment.

2.1.1. Steroidal antiandrogens in Japan

Cyproterone acetate, RU-486, and nilutamide are not approved in Japan for use in the treatment of patients with prostate cancer. On the other hand, chlormadinone acetate is approved in Japan but is not used in other countries. Evaluation of the relative efficacy and safety of these agents globally is therefore difficult. However, chlormadinone acetate has been reported to have advantages in terms of causing fewer adverse events. We therefore present information regarding chlormadinone acetate in this section.

Several Japanese groups have reported on the efficacy of chlormadinone acetate as an alternative antiandrogen therapy in the treatment of men with relapsed prostate cancer following first- or second-line hormonal therapy [21–23]. Steroidal antiandrogens including cyproterone acetate and chlormadinone acetate have also proven efficacious in the treatment of prostate cancer patients who suffer from hot flushes [24, 25]. However, Igawa et al. [26] reported that CAB therapy using chlormadinone acetate led to a significantly poorer survival outcome versus the use of bicalutamide. Nevertheless, because this survival trend was not observed in M0 cases, they concluded that chlormadinone acetate might still be an option for CAB therapy, depending on the clinical stage and the severity of adverse effects including hot flushes [26].

2.1.2. Clinical study and basic research

Ongoing clinical studies and basic research using chlormadinone are presented in **Table 1**. There has been at least one evaluation on whether low-dose chlormadinone has an effect on continued active surveillance (**Table 1**, No.1; UMIN000012284). Another study has evaluated whether chlormadinone has a more favorable effect on lipid and bone metabolism than that of bicalutamide (No.2; UMIN000018478). In terms of basic research, Koike et al. [27] have reported on the effects of chlormadinone acetate on the development and progression of prostate cancer in their *PTEN*-deficient mouse model (**Table 1**, No. 3). They demonstrated that chlormadinone acetate treatment suppressed the proliferation of cancer cells but did not decrease the development of prostatic intraepithelial neoplasia (PIN). This means that

chlormadinone did not act to prevent prostate cancer onset. The findings from this study suggest that inhibiting androgen signaling is effective in preventing the proliferation of prostate cancer caused by PTEN dysfunction. It has also been suggested that androgen plays an important role at the early stages of prostate cancer development in this mouse model [27].

	Clinical study	
No	**Concept and outline**	**Objectives**
1	Multicenter, randomized, double blind, placebo-controlled parallel group comparative study to evaluate the effect of low-dose chlormadinone acetate on the rate of continued active surveillance of patients with low-risk prostate cancer	To evaluate the effect of chlormadinone acetate on the rate of continued active surveillance by administration of low-dose chlormadinone acetate or placebo to patients with low-risk prostate cancer
2	Impact of endocrine therapy on lipid metabolism and bone metabolism of prostate cancer patients Comparison with chlormadinone acetate and bicalutamide	To investigate the effect of chlormadinone acetate and GnRH agonist combination therapy or bicalutamide and GnRH agonist combination therapy for prostate cancer men on lipid metabolism and bone metabolism
Basic research		
3	Conditional *PTEN*-deficient Mice as a Prostate Cancer Chemoprevention Model [27]	The potential of *PTEN*-deficient mice was examined by evaluating the chemopreventive efficacy of the anti-androgen, chlormadinone acetate

Table 1. Clinical studies and basic research on chlorm.

2.2. Nonsteroidal antiandrogens

The nonsteroidal antiandrogens, flutamide and bicalutamide, are well known in oncology and are major therapeutic tools in the treatment of prostate cancer patients. Therefore, information on their anticancer effects, including causation of decreases in serum prostate-specific antigen (PSA) levels and enhanced survival rates, has been presented in numerous reviews. There is

also a corresponding amount of literature on their adverse effects. Here, we introduce the clinical benefits and limitations of nonsteroidal antiandrogens in the treatment of CRPC patients.

2.2.1. Optional treatment for castration-resistant prostate cancer

Bicalutamide is the most common used steroidal antiandrogen due to its good curative effects and limited adverse effects. It is combined with luteinizing hormone-releasing hormone agonist/antagonist therapy to treat CRPC. Some researchers have indicated that dose elevation of antiandrogen agents may enhance their efficacy. For example, the routine dose of bicalutamide is 50 mg/day but evidence suggests that higher doses might be more effective [28]. Klotz et al. [29] reported that 22% of the patients showed a ≥50% decline in serum PSA levels following an increase in the dose of bicalutamide from 50 mg/day to 150 mg/day. Lodde et al. [30] reported the palliative benefits of 150 mg/day bicalutamide therapy in 44.7% of 38 CRPC nonmetastasis patients. These studies therefore demonstrate that a high proportion of CRPC patients could benefit from treatments involving elevated doses of steroidal antiandrogens. Available data also indicate that bicalutamide at a dose of much greater than 50 mg (at least 150 mg) daily in combination with castration may increase efficacy against CRPC progression. However, in all these studies earlier, either the median response duration is brief or the evaluation indices are limited.

Meanwhile, potential predictive factors for improved responses to high-dose (150 mg) bicalutamide therapy have been discussed. Qian et al. [28] suggested that secondary hormonal therapy with 150 mg bicalutamide daily was effective in patients with CRPC. Patients with a lower Gleason score, lower serum PSA concentrations, and who were using flutamide as a first-line nonsteroidal antiandrogen achieved more benefits when treated with bicalutamide 150 mg therapy. Patients with PSA decreases ≥85% had improved times of response to bicalutamide 150 mg therapy. Moreover, when compared with the common side effects of androgen-deprivation therapy, the adverse effects of bicalutamide 150 mg therapy were well-tolerated.

2.2.2. Combination with molecular target drugs

Angiogenesis, mediated by the vascular endothelial growth factor receptor (VEGFR) pathway, may be a good target for treatment of prostate cancer; it has been implicated in both the development and progression of the disease [31–33]. Studies have found that median levels of plasma VEGF are significantly higher in patients with metastatic prostate cancer when compared with those with localized cancer and that elevated plasma and urine levels of VEGF may be independent negative prognostic factors [34–36]. These findings suggest that inhibiting the VEGFR pathway might be an effective approach in prostate cancer.

In addition, the mammalian target-of-rapamycin (mTOR) is a critical molecule in controlling the proliferation of tumor cells. It can be activated by mutation or activation of signaling molecules such as PI3K or Akt. Alterations in the PI3K/Akt/mTOR pathway play an important role in prostate cancer, and it is estimated that upregulation occurs in 30–50% of prostate cancer

cases [37]. Recently, clinical trials on the efficacy and tolerability of antiandrogen and molecular target combination therapy have been conducted (**Table 2**), but these have included only a small number of patients. Results have shown that neither the PSA-response rate nor the PSA-progression free survival is fully satisfactory. In addition, peculiar adverse events have been associated with molecular target agents. Hence, these therapies are not currently in practical use.

Year	Molecular target therapy	N	Phase	PSA-RR	PSA-PFS	Ref
2012	Everolimus: 10 mg	36	II	5.6%	8.7 wks.	[33]
2012	Sorafenib: 400 mg	39	II			[38]
2013	Ridaforolimus: 30 mg	12	—	36%	—	[39]
2014	Vandetanib: 300 mg	19	II	18%	3.16 mos.	[40]
2015	Pazopanib: 800 mg	13	II	17%	—	[41]

N, number of patients; PSA, prostate specific antigen; RR, response rates; Ref, references; wks, weeks; mos, months.

*PSA response was defined as ≥ 50% decline.

**PSA response was defined as ≥ 30% decline.

Table 2. Combination therapy of bicalutamide and molecular target therapy for castration-resistant prostate cancer.

3. Estrogens and estrogen-based therapy

It is well-known that estrogens carry a significant risk for cardiovascular events. Androgen deprivation therapy is therefore the first choice as primary therapy for advanced prostate cancer. However, many authors have now investigated the anticancer effects of diethylstilbestrol [42], transdermal estradiol [43], and more recently, oral ethinylestradiol [44, 45] in the treatment of CRPC as well as in the treatment of hormone-naive prostate cancer. These authors have concluded that estrogen therapy is still relevant and can induce PSA response (50% PSA decline) rates as high as 69.6% in CRPC patients. Moreover, estrogen therapy is associated with fewer of the toxicities associated with ADT. It can maintain bone mineral density, suppress hot flushes, and improve cognitive function and lipo-metabolism in castrated men.

Estrogens inhibit the hypothalamic–pituitary–testicular axis through negative feedback mechanisms. Moreover, estrogen administration can induce a decrease in the levels of adrenal androgens and testosterone produced by the Leydig cells of the testes [46]. A direct cytotoxic effect of estrogens on prostate cancer cells has not been fully investigated. However, there are some reports on their cytotoxic effects on *in vivo* and *in vitro* castrate xenograft models [47, 48].

3.1. Diethylstilbestrol

Diethylstilbestrol (DES) is a synthetic estrogen. In the 1940s, Huggins and Hodges [49] reported that DES suppressed the progression of prostate cancer. DES was then used as a first-

line hormonal therapy for over 10 years in the treatment of prostate cancer patients. However, in 1970, increased mortality from cardiovascular and thromboembolic events associated with DES was reported in a prospective randomized controlled trial (VACURG study) [50]. Briefly, of the 1103 patients treated with DES (5 mg/daily) with no anticoagulation therapy, 17% of the patients died due to cardiovascular events (the mortality associated with cardiovascular event in the placebo group was 11.7%). Therefore, to suppress the risk of adverse events including cardiovascular disease, administration of lower doses of DES was investigated in clinical trials. However, although this approach significantly reduced cardiovascular morbidity, it was still higher than that associated with castration. For example, in the EORTC 30805 study, the cardiovascular mortality of the DES (1 mg/daily) and orchidectomy-alone groups was 14.8% and 8.3%, respectively [51]. Meanwhile, the cardiovascular toxicity of DES was significantly decreased by the use of anticoagulants such as warfarin or aspirin [52, 53]. From these facts, we note that DES treatment has a relatively high risk of cardiovascular events and that it must be used with anticoagulation therapy. On the other hand, we also understand that DES is one of the most effective and useful therapeutic options for prostate cancer patients as it can suppress cancer progression.

In terms of PSA response (>50% decline from baseline) to DES treatment in CRPC patients, approximately 40% patients were reported to be PSA responders [42, 54]. More recently, Wilkins et al. [55] disclosed results from a larger CRPC cohort (231 patients) treated with DES at a dose of 1–3 mg daily and with aspirin at 75 mg. They reported that the PSA response rate was 28.9% and that the median time to PSA progression was 4.6 months. These results cannot be considered satisfactory in terms of cancer control. However, interestingly, Wilkins et al. also reported that 18% of the patients showed an improvement in bone pain. Other investigators have also observed an improvement in certain types of pain in CRPC patients treated with DES [56]. Overall, DES remains a reasonable palliative option for patients with symptomatic CRPC even though its survival benefits may be limited. However, careful informed consent from the patients who are fully apprised of the cardiovascular risks associated with DES should be required.

3.2. Transdermal estradiol

As mentioned earlier, cardiovascular disease and thrombosis are the most dangerous adverse events associated with estrogen-based agents. In contrast to oral estrogens, parenterally administered estrogens do not increase liver protein synthesis and may be less prothrombotic [43]. In fact, in women who receive estrogen replacement therapy, the risk of cardiovascular events is increased with oral, but not transdermal, estradiol. There have been several informative studies about safety, potential side effects, and efficacy in the use of transdermal estradiol in the treatment of CRPC patients [43, 57]. In a Phase II study, CRPC patients suffering continued disease progression after primary hormonal therapy were treated with transdermal estradiol (0.6 mg per 24 h) [43]. Toxicity associated with the transdermal estradiol application was modest and no cardiovascular events occurred. In terms of cancer control, three of the 24 patients (12.5%) showed a PSA response. Another study analyzed the safety and efficacy of transdermal estradiol patch in the treatment of CRPC patients after ADT and chemotherapy

[57]. This study showed a PSA response rate of 10%. No cardiovascular events were observed. Thus, transdermal estrogen therapy was well-tolerated in the CRPC patients, and there were no significant cardiovascular complications. However, as with oral estradiol, the anticancer effects of transdermal estradiol appear to offer very limited survival benefit.

3.3. Ethinylestradiol

Treatment with ethinylestradiol was used in the 1980s as palliative therapy in patients with advanced prostate cancer. However, ethinylestradiol treatment has become less common since the development of newer treatment forms such as ADT [58]. On the other hand, one advantage of ethinylestradiol is that it is inexpensive. This is an important consideration in assessing treatment strategies. At present, ethinylestradiol is not used as a first-line hormonal therapy. However, it is still used as a second-line or a later option for CRPC patients [59]. Several investigators have reported on the efficacy and adverse events of ethinylestradiol in treatments of CRPC patients. For example, Onita et al. [60] reported that a decrease in serum PSA levels was seen in all 15 tested CRPC; 11 patients (73.3%) showed decreases of more than 50% without severe side effects. Other investigators have performed ethinylestradiol monotherapy at a dose of 1.5 mg/day for CRPC patients for whom more than one salvage therapy had not been effective [45]. In this retrospective study, the PSA response rate was 69.6%, and the median progression-free survival was estimated as 300 days. On the other hand, adverse events occurred in 3 of the 23 patients (13%). These adverse effects included elevation of liver enzymes, anorexia, and heart failure. Recently, results of a larger prospective study of ethinylestradiol monotherapy were reported [44]. In this study, 116 patients with metastatic CRPC were administered ethinylestradiol at a daily dose of 1 mg and with aspirin at a daily dose of 100 mg. A PSA response was observed in 79 patients (70.5%). PSA levels lower than 4 ng/mL in serum were observed in 24 patients (21.4%). Toxic adverse effects that required

	Year	N	Daily dose (mg)	PSA-RR (%)	PSA-PFS	Ref
Diethylstilbestrol	1998	21	1.0	42.9	—	[42]
Diethylstilbestrol	2000	34	1.0	NA	6 mos.	[54]
Diethylstilbestrol	2012	243	1.0–3.0	28.9	137 days	[55]
Trans. estradiol	2005	24	0.6	12.5	12 wks.	[56]
Trans. estradiol	2012	20	0.4	10.0	—	[57]
Ethinylestradiol	2003	10	1.0	90.0	12.0 mos	[59]
Ethinylestradiol	2009	18	1.0–3.0	73.3	15.0 mos	[60]
Ethinylestradiol	2010	24	1.5	69.6	300 days	[45]
Ethinylestradiol	2015	116	1.0	70.5	15.1 mos	[44]

N, number of patients; PSA, prostate specific antigen; RR, response rates; PFS, progression-free survival; Ref, references; mos, months; NA, not available; wks., weeks; Trans, transdermal.

*PSA response was defined as ≥50% decline.

Table 3. Summary of the anticancer effects in the studies of estrogens.

treatment cessation were described for 26 patients (23.2%). The main adverse effect requiring treatment cessation was thromboembolism (18 patients). Overall, however, no patient died as a result of treatment toxicity.

In addition to monotherapy, several clinical studies on combination therapies that include ethinylestradiol have been conducted. For example, in one small study, administration of 1 mg oral ethinylestradiol combined with lanreotide acetate (somatostatin analog) resulted in a decline in serum PSA levels of >50% in 9 out of the 10 CRPC patients (90%) [59]. Overall, administration of ethinylestradiol in CRPC cases resulted in a high percentage of PSA responses. The potential for cardiovascular toxicity could be managed through appropriate patient selection and concomitant anticoagulation therapy. A summary of the anticancer effects of estrogens is shown in **Table 3**.

4. Corticosteroids

Corticosteroids suppress the production of androgens from the adrenal gland through the regulation of the pituitary–adrenal axis. Consequently, corticosteroids can inhibit the malignant behavior and survival of prostate cancer cells. In addition to this indirect role, they are known to inhibit the growth of prostate cancer cells by interfering directly with a variety of cancer-related factors [61]. Recognizing this, corticosteroids have been used in cancer therapy for decades. They have been administered to prostate cancer patients both as a mono-therapy and in combination with other anticancer agents. Unfortunately, its anticancer effects, including prolongation of survival, are limited when used as a single agent [62]. In this section, we discuss corticosteroids in terms of their efficacy when used in combination therapy for the treatment of CRPC.

4.1. Which types of glucocorticoids are better?

A variety of glucocorticoids, including prednisone, prednisolone, hydrocortisone, and dexamethasone, have anticancer effects and associated clinical benefits for prostate cancer patients [63–65]. However, many investigators have suggested that their anticancer effects differ from each other. For example, the PSA response rates of prednisolone (5 mg × 2 =10 mg daily) and hydrocortisone (40 mg daily) administered to CRPC patients were reported to be 26% and 22%, respectively [66, 67]. In the case of prednisone, 34% of the patients had a decrease in PSA levels of more than 50% [64]. In the previous reports, PSA response rates associated with prednisone, prednisolone, and hydrocortisone treatments have ranged from 9 to 33% [68]. On the other hand, in the case of dexamethasone, decreases in PSA levels of ≥50% were detected in 50 of 102 (49%) of the CRPC patients treated at a dose of 0.5 mg daily [68]. Other investigators also reported a similar decrease in PSA levels in 61% of CRPC patients treated with dexamethasone at a dose of 1.5 mg or 2.25 mg daily [69]. Based on these reports, dexamethasone appears to have a significantly greater anticancer effect than other glucocorticoids [70]. However, one report indicated that dexamethasone at a dose of 1.5 mg daily showed a reduction of PSA levels of ≥50% in only 28% of the CRPC patients [70]. Thus,

there is no general agreement on what specific glucocorticoid should be recommended for the treatment of CRPC patients. Recently, the first head-to-head clinical comparison of prednisolone versus dexamethasone as monotherapies in the treatment of CRPC patients was conducted [68]. In this study, patients were randomized, in a 1:1:1 ratio, between administration of intermittent dexamethasone (8 mg twice daily for 3 days every 3 weeks), daily dexamethasone (0.5 mg once daily), and prednisolone (5 mg twice daily). The intermittent dexamethasone treatment was terminated mid-study due to a lack of observed antitumor activity. Thus, comparisons of anticancer effects were conducted only between the daily dexamethasone and prednisolone treatments. A decrease in PSA levels of ≥50% was detected in 16 of 39 (41%) of the dexamethasone-treated patients and in 8 of 36 (22%) prednisolone-treated patients. Although this difference did not approach statistical significance, the investigators concluded that dexamethasone might be a more effective treatment than prednisolone. Other investigators have supported this conclusion [70].

4.2. Combination with next-generation antiandrogens

One clinical study evaluated the anticancer effects and safety profile of abiraterone acetate when used in combination with prednisone as a means to suppress secondary mineralocorticoid excess [71]. Another study reported a reduction in the PSA levels >50% in CRPC patients treated with dexamethasone in addition to abiraterone acetate [71]. This report also demonstrated that the anticancer effects of combination therapy of abiraterone acetate and prednisone were detected regardless of prior dexamethasone exposure [71]. Furthermore, the PSA response rates, defined as a 50% or more reduction in PSA levels associated with dexamethasone and prednisolone were reported to be 47% and 24% (P = 0.05), respectively, in CRPC patients during a randomized Phase II trial [67]. Based on this, a hypothesis that a "steroid switch" from prednisone to dexamethasone would be effective in the treatment of CRPC patients with disease progression under abiraterone and prednisone treatment has been suggested [72]. In fact, one retrospective study of 30 CRPC patients who underwent such a "steroid switch" while abiraterone was administered, showed that durable PSA responses occurred in up to 40% of the patients [72]. In this study, the dosage of prednisolone or dexamethasone was 5 mg b.i.d and 0.5–1.0 mg daily.

4.3. Combination with immunotherapy

Sipuleucel-T is the recognized leading immunotherapeutic cancer vaccine (dendritic cell vaccine therapy). A variety of additional immunotherapeutic agents that can be used singly or combination therapy is currently under development. In fact, based on results from clinical trials, personalized peptide vaccination strategies that use multiple anticancer peptides has been reported to be effective and safe in CRPC patients [73, 74]. Several reports have also demonstrated that low-dose dexamethasone is a useful partner for personalized peptide vaccination in the treatment of CRPC. This is because dexamethasone does not suppress the immune system. Dexamethasone also exerts its anticancer effects in a direct manner as well as by reducing AR signaling [5, 75]. Recently, Phase II randomized controlled trials have demonstrated that immunotherapy that comprised personalized peptide vaccination and low-

dose dexamethasone was well-tolerated in chemotherapy-naive CRPC patients and yielded a better outcome when compared to the effects of dexamethasone alone [76]. In short, progression-free survival periods, as evaluated by serum PSA responses, with peptide vaccine + dexamethasone (n = 37) and dexamethasone alone (n = 35) were 22.0 and 7.0 months (P = 0.076), respectively. In addition, the median overall survival in patients treated with peptide vaccine + dexamethasone (73.9 months) was significantly longer (P = 0.00084) than those treated with dexamethasone alone (34.9 month)

4.4. Modulatory approach for castration-resistant prostate cancer

Dexamethasone is often used as a component of modular therapy approaches in the treatment of CRPC. The aim of the modulatory approach is to inhibit the malignant activities of cancer and stroma cells through regulation of a variety of different pathological features including cancer-related molecules, angiogenesis, inflammation, and altered immune responses.

The effect of a modular therapy consisting of capecitabine, pioglitazone (PPARα/γ receptor agonist), refecoxib (or etoricoxib, a cyclooxygenase (COX)-2 inhibitor), and dexamethasone on 36 patients with metastatic CRPC was analyzed [77]. One half of treated patients (n = 18) showed a biochemical response defined as a ≥25% PSA decrease. Median periods of progression-free and overall survival were 4 and 14.4 months, respectively [77]. Results from a study on a modulatory therapy comprising imatinib (a platelet derived growth factor receptor (PDGFR) inhibitor), pioglitazone, etoricoxib, dexamethasone, and low-dose treosulfan have also been reported [78]. In that Phase II study, the anticancer effects and adverse events of the modular therapy were assessed in 61 CRPC patients. A total of the 23 patients (37.7%) were reported as PSA responders. Median progression-free survival period was approximately 15 months. However, all the patients experienced one or more adverse events and 27 patients (41.5%) had serious events. The most frequent adverse event was peripheral edema (56.9%). Nausea (38.5%), fatigue (35.4%), and dyspnea (35.4%) were also common occurrences. One of key characteristics of CRPC is its heterogeneity. Therefore, a variety of different approaches is essential in controlling tumor growth and progression. Based on this, modulatory therapy would appear to be a useful strategy. However, in general, this approach has been associated with a relatively high frequency of adverse events. In this section, we emphasized the importance of dexamethasone because of its anticancer effects as a GR agonist and its suppression of a variety of adverse events.

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