Clinical Progression to Castration-Recurrent Prostate Cancer

Mark Pomerantz and Philip Kantoff

1 Introduction

Since Huggins and Hodges proved unequivocally that prostate cancer (CaP) regresses in the castrate state, androgen deprivation therapy (ADT) has been the cornerstone of treatment for advanced CaP (Huggins and Hodges 1941). This treatment strategy has taken many forms. Bilateral orchiectomy reliably diminishes androgen production and was the mainstay of treatment in the 1940s. In 1941, Huggins and Hodges published their seminal work showing that therapy with estrogen, in the form of diethylstilbestrol (DES), was as effective as orchiectomy (Huggins and Hodges 1941). Chemical castration via DES was widely used until the mid-1960s, when the estrogen formulation was directly compared to other strategies, including bilateral orchiectomy. DES was associated with an improved cancer-related mortality but worse overall survival, due primarily to increased cardiovascular side effects (The Veterans Administration Co-operative Urological Research Group 1967). Despite attempts to find a less toxic but effective dose, DES fell out of favor as an alternative to orchiectomy. In the 1980s, long-acting, synthetic luteinizing hormone-releasing hormone (LHRH) agonists were developed (Tolis et al. 1982). These agents have emerged as the predominant method for achieving castrate levels of androgen.

ADT is highly effective, capable of inducing regression of disease in over 90% of CaP patients (Prostate Cancer Trialists' Collaborative Group 2000; The Medical Research Council Prostate Cancer Working Party Investigators Group 1997). However, ADT is rarely curative. While the time in remission can vary markedly between patients, CaP invariably becomes refractory to surgical or chemical castration. This chapter will examine clinical progression from androgen dependence to androgen independence, focusing on the clinical factors associated with the

M. Pomerantz(✉)
Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Dana Bldg, Room 1230, Boston, MA 02115, USA, E-mail: Mark_Pomerantz@dfci.harvard.edu

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emergence of resistance, and the natural history of and treatment strategies for castration-resistant prostate cancer (CRPC).

2 Definition of Androgen-Independent Prostate Cancer

Castration recurrent prostate cancer (CRPC) denotes progression of disease despite chemical or surgical castration. Various terms have been used to describe this disease state, and most have limitations. "Hormone refractory prostate cancer" is a term commonly used but is often inaccurate. Many patients who progress on ADT may still respond to further hormonal manipulation, such as inhibition of ligand–androgen receptor interaction or suppression of adrenal androgens (Scher et al. 1995). The term androgen-independent prostate cancer (AIPC) also can be misleading. AIPC is "androgen independent" in the sense that CaP flourishes at castrate levels of androgen, but the disease remains to some extent dependent on signaling of the androgen receptor. "CRPC" has been adopted as the best descriptor, is becoming more widely used, and will serve as the term describing castrate-resistant disease in this chapter.

The Prostate Specific Antigen Working Group was organized in 1999 to establish a standard definition for progression of CaP in the castrate state and maintain consistency across clinical trials (Bubley et al. 1999). The group defined progression as an increase in radiographic measurements of soft tissue CaP metastases, an increase in the number of metastatic sites on bone scan, or two consecutive increases in prostate-specific antigen (PSA). Disease progression must occur after bilateral orchiectomy or in the setting of a serum testosterone of $\leq$50 ng/dl. These criteria broadly characterize CRPC, yet they do not neatly categorize all men with CRPC. The biology and natural history of CRPC can vary widely from patient to patient. Further categorization is necessary to better assess prognosis and optimal treatment for CRPC patients.

Prior to the era of widespread PSA testing, there was considerably more uniformity among CRPC patients. Since biomarkers such as PSA that herald the onset of advanced disease did not exist, surgical or chemical castration was rarely performed prior to the onset of CaP-related symptoms. Thus, virtually all men who developed CRPC reached this state in the setting of metastatic disease.

In the PSA era there is considerably more clinical diversity among CRPC patients, and the variation in clinical presentation at the onset of CRPC has important implications. Much of this heterogeneity is related to the substantial stage migration that has occurred since the introduction of PSA testing. The majority of PSA-screened CaP patients are treated with radical prostatectomy (RP) or radiation therapy (RT) for localized disease (Catalona et al. 1993; Farkas et al. 1998), and up to 40% of these patients experience biochemical recurrence, defined as a serial rise in PSA in the absence of clinical metastases (Moul 2000). A rise in PSA is their first manifestation of recurrence, usually occurring well before the onset of metastatic CaP. Despite a lack of convincing evidence of benefit

of early intervention, at least one-third of patients are treated with ADT within 5 years of PSA-only recurrence without evidence of metastases (Mehta et al. 2004). Analysis of the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database, a network of urologists at more than 30 community and academic urology practice sites, showed that the median time from biochemical recurrence to the initiation of ADT is approximately 9 months (Mehta et al. 2004). As a result of starting ADT early in the course of disease, a considerable number of patients develop CRPC before the onset of clinical progression. The natural history of this group of patients is different from that of CRPC patients with metastatic disease, as will be discussed later.

Another important factor dividing CRPC patients into separate biologic categories is responsiveness to secondary hormonal manipulations. One group of patients progresses despite castrate levels of testosterone but is still capable of responding to further hormonal manipulation. A second group is deemed insensitive to all forms of hormonal therapy and is truly "hormone refractory."

Finally, it is now well established that ADT in the neoadjuvant and adjuvant setting with radiation therapy (RT) improves outcomes compared with RT alone for those with intermediate- or high-risk CaP. Should these patients recur after treatment, ADT is often reinitiated. This introduces another factor distinguishing one group at risk for CRPC patient from another: those who have been exposed to ADT in the past versus those who have not. Some evidence suggests that such patients progress to CRPC more rapidly.

In short, CRPC can be loosely defined as progression of disease despite castrate levels of androgen. However, a more precise definition must take into account other factors. As will be discussed later, responsiveness to other hormonal manipulations, extent of disease, and timing of initial ADT affect progression from androgen-naïve to castration-resistant CaP. These distinctions also affect prognosis and treatment options.

3 Clinical Predictors for the Development of CRPC

In the PSA era, clinical progression from treatment for localized disease to prostate cancer-specific mortality (PCSM) typically begins with PSA recurrence, ultimately followed by development of metastases and death (Pound et al. 1999). Several retrospective and prospective studies have examined time to reach these three endpoints (The Medical Research Council Prostate Cancer Working Party Investigators Group 1997; Moul 2000; Messing et al. 1999). Meanwhile, sometime during this series of events, ADT is started and CRPC develops. The length of time between the start of ADT and the development of CRPC, as gauged by PSA levels, may influence the time to clinical progression or PCSM; there is evidence that the time to PSA progression on ADT has prognostic significance (Shulman and Benaim 2004; Svatek et al. 2006). Moreover, evaluating time to PSA progression on ADT may provide important insight into the biology of CaP, as PSA elevation is the first

indication of CaP growth in the castrate state. However, few studies have comprehensively examined time to ADT resistance as a clinical endpoint, and fewer still have completely captured the heterogeneity of patients developing CRPC.

A retrospective series of 553 patients treated with ADT at the Dana-Farber Cancer Institute (DFCI) is among the largest studies to date analyzing time to CRPC (Ross et al. 2008). Most in this cohort were treated in the setting of relapse after local treatment with RP or RT. Approximately half of the patients had developed metastatic disease by the time ADT was initiated, and 16% had previously received ADT as part of neoadjuvant and/or adjuvant treatment. With a median follow-up of over 5 years, the median time to PSA progression from the start of ADT was 23.7 months (Ross et al. 2008). Other, smaller studies have reported time to CRPC among ADT patients (Oefelein et al. 2002; Fowler et al. 1995). One retrospective analysis consisted of 245 patients with localized CaP and 78 patients with metastatic CaP followed at the University of Mississippi. Those with localized CaP were ineligible for definitive treatment with RP or RT due to advanced disease, age, or comorbidity. ADT was the initial CaP treatment for all patients. As in the DFCI cohort, PSA progression was analyzed as a clinical endpoint. Median time to CRPC was only 15 months in the nonmetastatic subgroup and 10 months in the metastatic subgroup.

The differences in outcome among these datasets reflect the heterogeneity of patients receiving ADT. Though Gleason scores appear similar across the two studies, shorter time to CRPC is related to the extent of disease at the start of ADT. Virtually all patients in the University of Mississippi cohort, for example, were diagnosed due to physical findings or CaP-related symptoms. The majority of patients classified as having "localized" disease had locally advanced disease, such as lymph node or seminal vesicle involvement (Fowler et al. 1995). The median pre-ADT PSA in the locally advanced group was 49 ng/mL, compared with 8.4 ng/mL in the DFCI subgroup without metastatic CaP. Overall, the differences across studies demonstrate how the development of CRPC is influenced by host factors. This observation was clearly demonstrated within each series, when patients who started ADT in the setting of metastases were directly compared with those who started before objective evidence of metastases. In each study, the extent of disease at the time of initiation of ADT significantly effected the time to development of CRPC (Ross et al. 2008; Fowler et al. 1995). The biological basis for this is not known, but it may be that advanced, metastatic tumors contain a higher number and/or proportion of cells whose growth is androgen independent, accounting for a more rapid detection of CRPC as these cells flourish.

Clinical parameters at the time of ADT initiation also predicted time to resistance in these studies. In the DFCI cohort, PSA $>$ 16.3 ng/mL was a predictor of CRPC ($p < 0.05$) (Ross et al. 2008). A higher PSA level, like metastatic disease itself, perhaps reflects a higher volume of disease, a larger volume of androgen-independent cells, and therefore shorter time to progression. However, this association was limited to only those patients without evidence of metastases at the ADT start date. A similar finding was reported in the University of Mississippi cohort. A direct correlation was noted between pretreatment PSA levels and time to PSA

elevation in the group with localized disease but not in the group with metastases (Fowler et al. 1995). Why this effect should be limited to those without evidence of metastases is less clear. Perhaps, once CaP tumors reach a volume detectable by CT or bone scan, absolute PSA value is a less meaningful surrogate for the size of the androgen-independent cell population. The presence of detectable metastatic tumors in itself may indicate that an appreciable number of castrate-resistant cells exist, regardless of PSA level.

Other pretreatment PSA parameters may provide a more accurate reflection of the biology of the disease and how quickly CRPC will emerge in the metastatic setting. In particular, a shorter PSA doubling time (PSADT) prior to ADT is associated with a shorter time to progression to CRPC. In the DFCI cohort, across both metastatic and nonmetastatic patients, those with a PSADT < 3 months prior to ADT experienced PSA progression sooner than those with a longer PSADT (median 12 months vs. 33 months, $p = 0.02$) (Ross et al. 2008). As will be discussed later, PSA kinetics are also strongly associated with clinical outcome in patients with CRPC. Another PSA parameter predicting development of CRPC is PSA nadir. A lower PSA nadir (0.2 ng/mL in the DFCI study) is associated with longer time to progression to CRPC when using PSA endpoints (Ross et al. 2008; Oefelein et al. 2002; Fowler et al. 1995).

Of note, Gleason score greater than 7 was associated with shorter time to CRPC among patients with metastatic disease in the DFCI cohort (Ross et al. 2008). This suggests that high-grade, androgen-naïve, metastatic CaP becomes resistant sooner than low- or intermediate-grade disease (Morote et al. 2005). Yet, this biologic event may not have significant clinical consequences. Gleason score is not consistently associated with survival in patients with metastatic disease starting ADT (Yossepowitch et al. 2007; Figg et al. 2004).

A particularly intriguing finding from the DFCI study suggests that prior ADT for local disease affects the development of CRPC. The median duration of neoadjuvant and adjuvant ADT was 8 months, and the median duration between completion of ADT as a part of local therapy and the beginning ADT for recurrence was about 22 months. Prior therapy was associated with shorter time to CRPC in metastatic and nonmetastatic patients, even when taking other established prognostic factors into account (Ross et al. 2008).

This suggests at least two possible models for CRPC. One is that time on ADT is "fixed" no matter when the ADT is administered. If a patient's disease is "calibrated" to become resistant after a biologically specified period of ADT, the duration of effective ADT can be divided into different segments, for example, a period of adjuvant therapy and a later period of salvage therapy. Time to CRPC is then dependent on the total time treatment was administered. Another possibility is that the time disease remains androgen-sensitive is "set" from the time of first exposure to ADT until the time of CRPC, and includes periods off treatment. In this scenario, adjuvant ADT and ADT after biochemical recurrence are, in effect, part of an intermittent ADT regimen, with a long interval between treatments.

Experience with intermittent androgen deprivation (IAD) informs this issue. Several phase II and phase III studies have examined the efficacy of administering

chemical castration for a proscribed period of time, then withholding treatment until disease progresses to a predetermined PSA threshold. It has been shown that the time from start of hormonal therapy until the development of CRPC is similar for both IAD and continuous ADT (Stewart et al. 2005). This is consistent with the aforementioned latter scenario. On the other hand, these data are not consistent with data from Radiation Therapy Oncology Group (RTOG) trial 86-10. In this trial, men with extensive local involvement of CaP were randomized to 4 months of neoadjuvant ADT followed by RT or RT alone (Pilepich et al. 2001). Secondary analysis was performed to assess overall and disease-specific survival among men in both treatment arms who ultimately required salvage ADT (Shipley et al. 2006). Outcomes were not significantly different between those who received neoadjuvant treatment and those who did not. Unlike the DFCI analysis, the study did not examine time to PSA recurrence and therefore did not capture the earliest marker for CRPC. The findings may not contradict one another. However, they do raise the possibility that there is a threshold duration of prior ADT, which does not compromise outcome. The median duration of neoadjuvant/adjuvant ADT in the DFCI series was twice as long as the length of ADT in the RTOG study.

Serum testosterone levels after castration levels may also be a significant predictor for development of CRPC. In a recent study, serial serum testosterone levels were measured over the first 6 months of ADT in nonmetastatic CaP patients. Patients were treated with LHRH agonist alone or in combination with an antiandrogen (Morote et al. 2007). Among those treated with LHRH agonist alone, time to CRPC was significantly shorter for those with a testosterone level greater than 32 ng/dL (88 months vs. 137 months). Interestingly, for patients receiving combined androgen blockade (LHRH agonist and antiandrogen), this difference was not seen, even for patients with a testosterone level greater than 50 ng/dL. This suggests that post-ADT testosterone levels can predict time to CRPC. This study also nicely demonstrates that CRPC patients are not necessarily "hormone refractory." Further manipulation of the androgen axis, in this case with an antiandrogen, may provide further benefit to the CRPC patient.

In summary, patients are started on ADT at widely varying stages of their disease. This significantly influences the development of resistance to castrate levels of testosterone. The extent of disease, PSA parameters, Gleason score, previous exposure to ADT, and adrogen levels are factors that may impact the time to CRPC.

4 CRPC Natural History and Predictors of Clinical Outcome

Once CRPC develops, insight into its natural history and predictors of clinical outcome are valuable and may help direct treatment decisions. Extent of disease is, again, a critical consideration and influences the natural history of castrate-resistant disease. Patients with PSA-only CRPC appear to have a better outcome compared than patients with CRPC that develops in the setting of metastases. However, PSA-

only CRPC is a relatively new entity, a result of changing practice patterns in the PSA era. Few studies have focused directly on CRPC patients with no clinical evidence of disease.

The most thorough examination of this patient population was performed as part of an aborted study evaluating the effect of zoledronic acid on time to bone metastases in men with PSA-only CRPC (Smith et al. 2005). The study was closed due to a lower than expected event rate, but valuable insight was gained into the natural history of CRPC in the absence of clinical disease. The study enrolled 201 CRPC patients and at 2 years, only 33% developed bone metastases. Median metastasis-free survival was 907 days, and median overall survival was not reached at 2-years follow-up. The relatively indolent nature of disease in this study stands in contrast to CRPC in the setting of metastasis, as discussed later. It should be noted, however, that interventions with secondary hormonal therapy or chemotherapy were not documented in this cohort. It is therefore unknown if further therapeutic interventions contributed to outcome.

PSA levels were well annotated in this study and served as useful predictors of outcome. A longer PSA doubling time, for example, was associated with metastasis-free survival – a parameter that is also a strong predictor of outcome in hormone-sensitive CaP (D'Amico et al. 2003). In multivariate analysis, PSA $>$ 10 ng/mL and increased PSA velocity were associated with shorter time to first metastasis and were predictive of overall survival (Smith et al. 2005). Notably, PSA velocity was also found to be associated with mortality in a similar cohort of CRPC patients analyzed by D'Amico et al. (2005). Patients in this cohort, assembled from two multi-institutional databases, started ADT for PSA recurrence after RP or RT and ultimately developed CRPC. PSA velocity greater than 1.5 ng/mL/year after the start of ADT was associated with increased risk for all-cause and prostate cancer-specific mortality.

The natural history of metastatic CRPC has been more widely studied, though it is important to note that even within this population of CRPC patients, there is considerable clinical variability. Much of the data concerning the metastatic CRPC is derived from several studies enrolling a high percentage of patients with significantly advanced disease (Scher et al. 1999; Vollmer et al. 1998; Kantoff et al. 1999; Tannock et al. 2004; Petrylak et al. 2004). Two groups collected data from several such trials to describe the clinical course of metastatic CRPC and to define predictors of outcome (Smaletz et al. 2002; Halabi et al. 2003). The first analysis was derived from clinical series at Memorial Sloan-Kettering Cancer Center (MSKCC). A total of 409 patients were included in a discovery set and 433 in a validation set. Median survival across both groups was less than 16 months (Smaletz et al. 2002). The second analysis was based on a collection of six studies conducted by the Cancer and Leukemia Group B (CALGB). A total of 760 patients were included in the learning sample and 341 in a validation sample. Median survival across these groups was 13 months after a follow-up of 37 months (Halabi et al. 2003).

Predictors for survival after multivariable analysis from each study were used to develop nomograms. Both studies found poor performance status, lower

hemoglobin, higher LDH, and higher alkaline phosphatase to be associated with poorer overall survival. The CALGB study also incorporated Gleason score >7 and presence of visceral metastases into its nomogram, while the MSKCC study did not find that these parameters added information to their model. The MSKCC nomogram included age and levels of albumin, while the CALGB model did not.

A higher PSA prior to treatment for CRPC correlated with worse outcome in the MSKCC study, but the effect was very slight. In fact, when comparing the 25% and 75% PSA quartiles, no difference in survival was seen (Smaletz et al. 2002). In an analysis of 143 CRPC cases from DFCI, higher PSA levels predicted *improved* survival for men with bone metastases and a normal alkaline phosphatase (Xie et al. 2007). PSA in this setting may be a surrogate for two competing biologic processes. On the one hand, a higher PSA represents progressive disease, greater tumor volume and, as a result, worse outcome. As such, PSA also may be associated with worse performance status, higher LDH, and lower hemoglobin – parameters that directly correlate with outcome. On the other hand, a higher PSA may be associated with a more differentiated tumor, and a tumor with greater proportion of androgen-dependent cells. At an advanced stage of disease, this could represent a more favorable biology. Also, PSA itself is reported to have antiangiogenic properties (Balk et al. 2003). Finally, PSA has been implicated in the degradation of PTHrP (Balk et al. 2003), perhaps accounting for the normal alkaline phosphatase observed in the subset of patients in whom PSA appeared protective.

The MSKCC and CALGB studies only analyzed single, static PSA levels (Smaletz et al. 2002; Halabi et al. 2003). Since the publication of these studies, numerous groups have demonstrated the predictive value of PSA kinetics. In one series of 160 CRPC patients diagnosed in the PSA era, PSA doubling time was the variable most strongly associated with prostate cancer-specific survival (Shulman and Benaim 2004). Investigators divided the cohort into risk groups and highlighted the heterogeneity in presentation and prognosis among CRPC patients with advanced disease. The group with the most favorable PSA parameters, men with a PSADT >6 months, had a median cancer-specific survival of 89.1 months. Those in the highest risk grouping, which included men with a PSADT <6 months, had a median cancer-specific survival of 14.0 months. Unlike the MSKCC and CALGB studies, no patient in this cohort received cytotoxic therapy, suggesting that castration-resistant disease was discovered relatively early in its course. Likewise, in a similar cohort of 129 men with untreated CRPC, median overall survival was 52 months, and PSADT remained a statistically significant predictor of survival in multivariate models (Svatek et al. 2006).

Two recent studies evaluated survival in more advanced CRPC patients, those about to receive chemotherapy (Oudard et al. 2007; Armstrong et al. 2007). These series are particularly informative since most patients received docetaxel-based chemotherapy, the contemporary standard of care. The first study involved a cohort of 250 patients. For patients with a PSADT <45 days, median survival was 16.5 months and with a PSADT of >45 days it was 26.4 months (Oudard et al. 2007). The second study analyzed the cohort from the TAX327 trial, comparing docetaxel-based regimens to mitoxantrone. PSADT was separated into quintiles.

Median survival for patients with a PSADT <1 month was 13.3 months, and for patients with a PSADT >6 months median survival had not yet been reached (mean survival 22.5 months) (Armstrong et al. 2007).

5 Treatment of CRPC

As described earlier, the clinical course of CRPC may vary considerably. As such, treatment should be individualized based on a variety of factors including the presence or absence of metastases, performance status, and PSA kinetics. However, choosing an appropriate treatment for a particular patient can be challenging since there is an absence of survival data for most CRPC therapies. Moreover, CRPC is a difficult condition to evaluate via clinical trials. Overall survival is the most meaningful clinical parameter, but may not be a realistic study endpoint given the long natural history of many with CRPC, particularly those with PSA-only recurrence. Surrogates for survival in CaP have limitations. Compared with most other common cancers, CaP develops few soft tissue lesions measurable by radiograph. The most common site of CaP metastasis is bone, and bone scans are ill suited for accurately measuring changes in disease and are subject to interobserver variation. PSA would seem a worthy surrogate marker in light of the data emerging from CRPC series, as shown earlier. In addition, there are clinical data suggesting that treatment-induced PSA decreases $\geq$50% confer a survival advantage (Scher et al. 1997; Small et al. 2004). Yet there remains a lack of consensus regarding the best use of PSA, and no prospective trial data are available to resolve the issue.

There may be a patient population in which a watchful waiting approach is appropriate. CRPC patients with PSA-only recurrence after ADT may experience prolonged metastasis-free survival, particularly in the setting of favorable predictors, such as a long PSA doubling time (Smith et al. 2005). At the opposite extreme, cytotoxic therapy may be indicated for patients with rapidly progressive, symptomatic disease. In particular, docetaxel-based therapy has been clearly shown to improve survival and quality of life in this population (Tannock et al. 2004; Petrylak et al. 2004). For the large number of CRPC patients with a disease profile somewhere in between these two scenarios, a secondary hormonal manipulation may be the treatment of choice.

When initiating secondary hormonal treatment, it is helpful to consider the pathophysiology of CRPC. Despite the use of the term "androgen independence" to describe this disease state, the androgen axis remains involved in disease progression. In fact, the androgen axis often appears hyperactive in this disease state, and androgen receptor is consistently overexpressed in CRPC (Chen et al. 2004). Thus, relatively low levels of serum and intraprostatic androgen are required to promote disease progression. Moreover, mutations in the androgen receptor have been described, and certain mutations may confer a growth advantage to a given CaP clone (Taplin et al. 1995). The androgen axis hyperactivity may also result from alterations in cofactor expression, increased ligand promiscuity on the part of

the androgen receptor, or complete independence from ligand-receptor binding (Feldman and Feldman 2001).

Because the androgen axis remains very active in CRPC and is helping drive disease progression, ADT must be maintained no matter which treatment course is chosen, including watchful waiting. Though prospective data are lacking, there appears to be benefit in minimizing the ligand available to the androgen receptor. In a retrospective analysis of 341 patients treated in four randomized controlled trials for CRPC, continued androgen suppression was an independent predictor of survival (Taylor et al. 1993).

While secondary hormonal therapies have several mechanisms of action, there are two main methods by which these treatments take advantage of the cancer's continued dependency on the androgen pathway: antagonism of the androgen receptor (AR) and decrease in adrenal androgen production. For patients progressing after LHRH agonist or bilateral orchiectomy alone, AR antagonism with nonsteroidal antiandrogens is the strategy of choice. In a series of over 200 patients receiving the antiandrogen flutamide for metastatic CRPC, response rate was 34.5% and mean duration of response was 24 months (Labrie et al. 1988).

Among patients progressing while receiving an antiandrogen (either as part of initial treatment or as salvage treatment) up to 20% experience a greater than 50% decrease in PSA in response to withdrawal of the antiandrogen (Small and Carroll 1994; Small and Vogelzang 1997). The withdrawal effect occurs because the antiandrogen, which once served as an antagonist of the androgen receptor, begins to act as an agonist. It has been shown that over time antiandrogens select for androgen receptor mutations, fundamentally changing their effects. However, this may not be the mechanism of action in all cases (Taplin et al. 1999). Response, when it occurs, generally lasts 3–5 months before further progression. Despite the low rates of withdrawal response, almost all CRPC patients should be given a trial period off antiandrogen before new therapy is started.

This transformation from inhibition to activation appears to be a molecular event specific to each individual antiandrogen agent. This is evidenced by the fact that many patients respond to a second antiandrogen after failing a prior one. High doses of the antiandrogen bicalutamide (150–200 mg) are capable of inducing responses in patients who progressed on flutamide (Scher et al. 1997; Joyce et al. 1998). The antiandrogen nilutamide is also effective as a second line antiandrogen. In one study, this agent induced a nearly 50% reduction in PSA in 27% of patients whose disease had progressed on flutamide or bicalutamide (Kassouf et al. 2003).

Since the androgen receptor remains active in the setting of CRPC, further suppression of circulating androgen has therapeutic potential. This has been demonstrated with the administration of cytochrome P450 inhibitors, agents that block steroidogenesis in the adrenal gland as well as the testes (Pont et al. 1982). The adrenal gland is the source of approximately 10% of androgen production. The antifungal drug ketoconazole is the most widely used regimen in this class. A phase III trial randomized 260 CRPC patients to antiandrogen withdrawal or antiandrogen withdrawal followed by high-dose ketoconazole 400 mg three times daily with hydrocortisone (Small et al. 2004). Hydrocortisone is routinely included in this

regimen to prevent adrenal insufficiency. Those progressing on withdrawal alone arm were allowed to receive deferred ketoconazole. PSA response rates were 27% in the ketoconazole arm and 32% when including the patients receiving deferred treatment. Other trials using intermediate to high doses of ketoconazole have shown $\geq$50% reduction in PSA in 28–62% of patients (Small et al. 1997; Millikan et al. 2001; Nakabayashi et al. 2006). The agent abiraterone is also a potent inhibitor of adrenal androgen steroidogenesis. It is more focused than ketoconazole, specifically targeting 17-alpha hydroxylase and C17,20-lyase. Early clinical data suggest a profound effect on androgen production, and clinical trials utilizing this agent in patients with CRPC are ongoing (Taplin 2007).

Estrogens have known activity in CRPC, a phenomenon reported as early as the 1950s, when Nesbit and Baum reported a 17% response rate in this setting (Nesbit and Baum 1950). Several studies have since demonstrated estrogen's effects in CRPC, including several in the PSA era (Oh 2002). Estrogens are administered in several forms – diethylstilbestrol (DES), transdermal estradiol, conjugated estrogens (Premarin), and, though no longer available, PC-SPES. Estrogens exert their effects though multiple mechanisms. There is estrogen-mediated inhibition of the pituitary release of gonadotropins, which blocks testosterone production by the testes. It appears unlikely, however, that further decrease in circulating testosterone beyond that achieved by an LHRH agonist is clinically meaningful in CRPC. There is also evidence that estrogen treatment leads to a decrease in adrenal androgen precursors, suggesting a mechanism similar to ketoconazole (Takezawa et al. 2001; Kitahara et al. 1997).

The side effects associated with estrogen therapy can be significant. Thomboembolic and cardiovascular events are not uncommon, and even attempts to utilize a lower dose of estrogen (DES 1 mg) result in event rates between 5 and 18% (Oh 2002). Nonetheless, estrogens can induce responses in CRPC, and side effects may be manageable when patients are carefully monitored and treated with antithrombosis prophylaxis. In the PSA era, Smith et al. administered 1-mg DES and reported a 43% PSA response rate in 21 CRPC patients with a 5% rate of deep venous thrombosis (Smith et al. 1998). More recently, 90 CRPC patients were randomized in a phase II crossover study to 3-mg DES or the estrogenic herbal formulation, PC-SPES. PSA response to DES was 24% with a thromboembolism rate of 9% after low-dose warfarin prophylaxis (Oh et al. 2004).

Less data are available for other estrogen formulations. Transdermal estrogens have an improved safety profile, and no thromboembolic events were noted across two studies following a total of 44 patients (Ockrim et al. 2003; Bland et al. 2005). However, PSA response rates were poor, only 12.5% in one study (Bland et al. 2005). Premarin is composed of conjugated estrogens and has been widely studied as hormone replacement therapy in postmenopausal women. In a phase II trial including 45 CRPC patients, PSA declines of greater than 50% were seen in 25% receiving high-dose Premarin (1.25 mg three times daily) (Pomerantz et al. 2007).

Efforts are ongoing to improve the effectiveness of secondary hormonal manipulations. Several agents were developed to better utilize the mechanisms of action described earlier. For example, new androgen receptor antagonists are in early

phase clinical trials. Other novel agents alter downstream functions of AR. Hsp-90 inhibitors, for example, block a protein–protein interaction necessary for proper AR protein folding (Taplin 2007).

6 Summary

The emergence of CRPC marks a critical juncture in the clinical course of the disease. Host factors such as extent of disease significantly impact the development of CRPC. Several clinical parameters, such as PSA kinetics, are associated with time to CRPC and the natural history of CRPC once it develops. For patients whose disease is not rapidly progressive or symptomatic, CRPC may be susceptible to secondary hormonal treatment, a therapy generally less toxic that chemotherapy. Secondary hormonal treatments take advantage of CaP's continued dependence on the androgen axis. The markers for CRPC development and prognosis and secondary hormonal treatments become useful as increasing number of patients develop CRPC in the absence of any other signs of clinical progression.

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