Androgen Ablation Therapy and Prostate Cancer: An Update

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Authors’ contributions

This work was carried out in collaboration between all authors. Author MO designed the study, formatted the work, and wrote the first draft of the manuscript. Authors ME and OBO managed the analyses of the study and the literature searches. All authors read and approved the final manuscript.

ABSTRACT

It is now generally accepted that prostate cancer is the leading form of cancer in men. Current evidence indicates that countries including America and West Africa have more cases of aggressive progressive prostate cancer. Many treatment strategies have been used in management of prostate cancer. Since the discovery of androgen deprivation protocol seventy years ago, more treatment strategies have been reported which added more values to treatment outcome. However, death from this disease is due to resistance to androgen ablation therapy (AAT). Until recently, treatment of patients with disseminated prostate cancer was based on modalities that reduce AR signalling, either by direct androgen depletion (castration, e.g., surgical orchietomy, luteinizing hormone-releasing hormone agonists), by blockade of the androgen receptor (AR) (e.g., flutamide, bicalutamide), or by combinations. In literature there is wide range of reports on diverse treatment strategies for prostate cancer; this often lead to serious confusion among clinicians and scientists, especially those new to the field. This study reviewed all the current available treatment strategies for androgen ablation therapy in management of hormone sensitive progressive prostate cancer, and highlights the merits and challenges involved in each of the treatments options. Thus, providing a...
summary of wide range of available literature on hormone management of prostate
cancer and brings the scientists and clinicians to a focus using the best available
evidence-based approach.

Keywords: Prostate cancer; androgen ablation; gonadotropins and castration.

1. INTRODUCTION

Recent epidemiological studies of prostate cancer have shown that it is the most common
form of cancer in men in the United State of America, and the second leading cause of death
due to cancer, [1]. Approximately 100 men are being diagnosed with this disease daily in the
United Kingdom [2]. There are many factors that contribute to the development of prostate
cancer; the most important of them are age, diet, ethnicity environment and genetic
inheritance, [3]. For instance, men at older age are commonly diagnosed with advanced
disease while the early form the disease is seen at younger age, (Nelson et al 2003). In
both American and British studies, men of African descendant, or who emigrated from Africa,
had increased risk of being diagnosed with this disease [1,2 ].

The androgen receptors located inside the cytoplasm of the prostate cells have stronger
affinity for dihydrotestosterone DHT and binds to it [4]. This results in phosphorylation and
dimerization that lead translocation of the complex to the nucleus [5] where it binds to the
androgen response – element of the DNA [4]. Clearly, these events initiate transcription of
specific genes required for cell growth and development. The understanding of the
endocrine role of DHT and prostate growth and development paved the way for hormonal
treatment of prostate cancer through manipulating its effect on the gland. This is the
rationale for treatment of prostate cancer using androgen ablation therapy to manipulate or
inhibit some stages in the hypothalamus pituitary gonadal axis, thereby depriving the
prostate of its required hormones for growth and development.

Cancerous growth in human prostate gland is known to interfere with normal prostate
biology; specifically, this often affects the secretion of prostate specific antigen (PSA) and
the entire architecture of the gland – this would depend largely on the Gleason score of the
grade of the tumour [4]. Fig. 1 highlights specific cellular changes or histological changes
that may characterise the glandular structure of cancerous prostatic epithelia in comparison
to a normal prostate gland. Such changes in the tumour microenvironment may contribute to
the various signs and symptoms and even the molecular signature of prostate cancer.

There is increased number of literature on management of prostate cancer; these range
from articles, opinions, reviews and editorials. These often keep readers and practitioners,
and even the new entrants into the field very confused. The aim of the current study is to
bring together all these diverse available data to provide a synthesis that brings scientists
and clinicians and indeed the general public to a focus; and to provide an update in hormone
management of prostate cancer.
Fig. 1. Immunohistochemical staining for E-cadherin showing secretory glandular structure (left) in the normal prostate and how it is disrupted in invasive prostate cancer (right), by suppressing PSA production by androgen ablation therapy, the glandular architecture can be reverted and the E-cadherin expression may also increase. [4]

2. MANAGEMENT OF PROSTATE CANCER

For men with localized prostate cancer, common treatment options include watchful waiting, surgery to remove the prostate gland (radical prostatectomy), external beam radiation therapy (EBRT), cryotherapy and androgen-ablation therapy, [6].

Available randomised controlled trial on the treatment of prostate cancer has not recommended a particular method for treatment. However, [7,8], in randomised trials respectively compared the radical prostatectomy with watchful waiting in patients with early prostate cancer, and found that radical prostatectomy reduced disease specific mortality significantly compared to watchful waiting, but has no effect on the overall survival,[9,10], compared the effect of immediate and delayed treatment with anti-androgen therapy in patients with minimal residual disease after prostatectomy in advanced prostate cancer, and demonstrated that immediate therapy with antiandrogen after radical prostatectomy and pelvic lymphadenectomy improved end points and reduced recurrence. On the contrary, a systematic review of Randomized Controlled Trials (RCTs) and observational studies found no clear cut evidence for any one treatment option; and that the quality of life was higher in the watchful waiting than in surgical interventions [11]. Best method for treating patients with prostate cancer is currently subject of controversy. It may therefore be reasonable to apply watchful waiting approach in patients with early stage or low Gleason score; and in those with low life expectancy [12]. However, in many practices, patients are provided with various options and allowed to make decision with their Physician.

In this work, we focused on androgen ablation therapy as a better option for management of androgen dependent localized prostate cancer and reviewed various treatment options in the protocol.
2.1 Androgen Ablation Therapy

Not until 1941 when Huggins and Hodges published their study on the effects of hormone deprivation in men with prostate cancer, nothing was really known about androgen ablation therapy (AAT) or androgen deprivation [13]. Since then, management of advanced prostate cancer has experienced progressive modifications and improvements. To date, AAT has become the mainstay in the treatment of advanced prostate cancer. This method has been shown to improve the quality of life in more than 80% of patients with advanced prostate cancer; however, the median duration of this benefit was only two to three years [14], before the emergence of androgen resistance state [15].

2.1.1 Types of androgen ablation therapy

Androgen ablation can be administered by orchiectomy (castration) or medically (chemical castration). The surgical method involves either the unilateral or bilateral removal of the testicles [16]. The medical castration is normally achieved by manipulation of the male hormonal axis (Fig. 2), with resultant drop in the level of prostate specific antigen PSA, and a substantial palliative benefits [15]. The major aim of androgen ablation therapy is to down-regulate or shut the androgen production. This is normally achieved by the use of synthetic analogues of gonadotropin-releasing hormone GnRH (also known as luteinising hormone releasing hormone agonists, LH-RH) and antagonists to suppress testicular function [16]; (figure.3 and 5). Since the testis is not the only source of androgen, a continuous stimulation of the cells by androgen from adrenals during the initial therapy has been observed [15]. In other to effectively counteract the adrenal and testicular androgen production, the use of androgen receptor blockers or antiandrogens such as flutamide, cyproterone acetate, or nilutamide and bicalutamide are well documented [14]. Other members of this class are maximal androgen blockade and 5α reductase inhibitors, gonadotrophin releasing hormone antagonists, and estrogens.

Fig. 2. The hypothalamic–pituitary–gonadal axis. The pituitary gland controls the secretion of FSH and LH. The gonadotropins regulate function of the testes. AAT involves the manipulation of this axis. E; estrogen, P; progesterone, T; testosterone [17]
2.1.2 Diethylstilbestrol (DES)

Diethylstilbestrol is an estrogen that suppresses the pituitary–gonadal axis (Fig. 2). This agent was the earliest estrogen agent used in androgen ablation protocol in management of advanced prostate cancer, [18,19]. The use DES for AAT has been shown to result in a total testosterone blockade by selectively blocking binding of luteining hormone (LH) without affecting follicular stimulating hormone, [14]. Due to safety issues regarding this agent especially its association with cardiovascular toxicity [20], and cardiovascular death at optimum dose of 5mg [18], its clinical application was gradually reduced [19]. Currently, there are large volumes of evidences showing that not only does DES provide effective androgen deprivation, but also its estrogenic metabolite (2-methoxyestradiol) has significant antiangiogenic and pro-apoptotic effects; and suppresses extra testicular testosterone production even in androgen refractory prostate cancer; with a median response time of 5 to 9 months [19,21,22]. This persuasive report may warrant a choice for DES in high Gleason score or highly progressive prostate cancer.

Furthermore, benefits of the use of DES also included the observation of similar effects as orchiectomy with a response rate of 40 – 60% within 5 to 8 months; and adverse effects in 10 to 30% of patients [19]. When DES was compare with casodex for management of refractory prostate disease, [23] found that DES had same efficacy as Casodex in reducing serum PSA level and a shorter response time of 9 months, against 12 months in Casodex treated group. Unfortunately, there are sufficient evidences indicating that DES has more adverse effects; including loss of libido, impotence, cardiovascular toxicity compared to Casodex [19].

2.1.3 Gonadotropin-releasing hormone GnRH agonist

Androgen ablation therapy using GnRH agonist is one of the techniques in achieving medical castration. Leuprolide and goserelin are commonly used GnRH. Its administration is usually staggered (for example, day 1-, 3-, 4-, and 6-month depot injections) and within the first two weeks of administration, the serum concentration of androgen spikes [14,24] see Fig. 3 below - the solid lines). Luteining hormone is usually released from the pituitary in a pulsatile manner (Fig. 3), and acts directly on the leydig cells of the male gonad and stimulates them to produce testosterone [25]. However, prolonged administration of GnRH, down-regulates the GnRH receptors in the pituitary; causing a complete occupation of the receptors and shuts the synthesis and secretion of gonadotropins (Fig. 3); and a subsequent decrease of androgen production to a castration level (50 ng/dL or 1.7 nmol/L) within three weeks [24]. This approach normally results in the reduction of activation of androgen receptors by approximately >90%; and also causing estrogen levels to decrease by >80% in most patients [14,25].

Flare reaction has been reported as the main drawback using this agent. This reaction may worsen symptoms and results in death of some patients [14,24,26]. Hence, more serious adverse effects have been extensively reported, and include hot flushes, impotence, anaemia [14,15].

2.1.4 GnRH antagonists

Gonadotropin releasing hormone agonist; for instance, Abarilex has been shown to have higher efficacy in achieving optimum chemical castration compared with an agonist like leuprolide (Fig. 3). There is no initial flare reaction, even in patients with severe symptoms of
advanced prostate cancer who may have serious adverse effects of the flare phenomenon when agonist is used [24]. Using this method, 72% of patients achieve castration level of testosterone within 8 days and the prostate volume reduced by 19 to 46%; while the PSA will decreases in 10 days [14]. However, the adverse effects of this agent are huge and include anaphylaxis [24], loss of libido, and impotence [14,15,17,27].

**Fig. 3. Serum testosterone levels following treatment with GnRH in patients with prostate cancer, comparing the efficacy of leuprolide and bicalutamide solid lines and the abarilex in achieving castration level. [17]**

Furthermore, a recent guidelines on the evidence based-management of prostate cancer using androgen ablation therapy (AAT), clearly reiterate that the primary objective of hormonal therapy is to slow down the progression of the disease to the greatest possible extent. To achieve this aim, Degarelix, a new product for the treatment of hormone-dependent Pca. has recently become available in some countries. This product is classified as a GnRH antagonist and provides safe and effective ADT. It completely blocks the synthesis and release of gonadotropins (LH and FSH), thus rapidly reducing the testosterone levels without causing clinical flare [28]. Evidence from a recent clinical trials (36 months) demonstrate that degarelix, compared to high-dose leuproprelin (7.5 mg), suppresses levels of testosterone and PSA more rapidly, and reduces levels of FSH and musculoskeletal events associated with treatment (pain, muscle weakness, spasms, oedema/joint stiffness, arthralgia, osteoporosis and osteopenia) to a greater extent [29].

In addition, there are sufficient published works that demonstrate a significant increase in the probability of PSA progression-free survival using Degarelix suggesting a possible delay in the onset of the androgen resistance or castration-resistant stage [28,29,30]. In fact a most recent phase II randomized multicenter study that evaluated the safety and efficacy of Degarelix showed that monthly degarelix dosing was effective in achieving testosterone suppression without a testosterone surge, prostate-specific antigen reductions and antitumour effect in Japanese patients with prostate cancer [30]; this result was also confirmed in a Phase III study. In the study of [30], patients treated with dose regimens of 240/80 and 240/160 mg maintained castrate levels of testosterone in 94.5 and 95.2% of the patients, respectively. After 3 days, 99.3 and 98.5% of the patients, respectively, reached these levels without a testosterone surge. Prostate-specific antigen levels decreased rapidly following degarelix administration and remained low throughout the study [30]. The findings of that
study strongly confirmed a previous report by [31] who demonstrated a statistically significant prostate specific antigen progression-free survival benefit for degarelix over leuprolide and suggested that use of degarelix may be regarded as first line androgen deprivation therapy as an alternative to a gonadotropin-releasing hormone agonist. The information available to date supports the use of this new molecule as a valid alternative to GnRH agonists in the treatment of hormone-sensitive PCa.

2.1.5 5α-Reductase Inhibitor (5-ARI)

This is the major enzyme in the cytoplasm of the prostatic cells that converts testosterone to DHT and estradiol. Finasteride is the main agent in this group; however, its utility in the management of prostate cancer including androgen ablation therapy is not established. Importantly, 5-ARIs are especially recommended for prostates greater than 40ml and PSA greater than 1.5ng/ml. Ordinarily, the initial management for increased prostate volume would includes lifestyle modification, and smooth muscle relaxant alpha blocker therapy [32]. Alpha blockers usually take effect quickly within 3-5 days, and have minimal side effects. Current commonly used alpha blockers include the selective alpha blockers tamsulosin (Flomax), alfusosin (Xatral), and silodosin (Rapafllo). For patients with larger prostates, the 5-alpha reductase inhibitor class (finasteride (Proscar) and dutasteride (Avodart)) work effectively to shrink prostate stroma resulting in improved voiding [33]. The 5-ARI class of drugs, in addition to reducing prostate size, also reduce the need for future surgery, and reduce the risk of future urinary retention [33]. Furthermore, a recent study found that treatment of prostate cancer with Dutasteride significantly delayed the time to PSA doubling compared with placebo after 24 mo of treatment (p<0.001); the relative risk (RR) reduction was 66.1% (95% confidence interval [CI], 50.35-76.90) for the overall study period [32].

Available data indicate that finasteride blocks only type 2 isoenzyme thereby causing a 70 % reduction in production of DHT, while Dutasteride blocks both type 1 and 2 isoenzyme resulting in up to 90% reduction in DHT production [33]; this strongly suggest that Dutasteride may have dual action which may lead to faster clinical effect. However, adverse effect associated with the 5ARI include mild erectile dysfunction, decrease libido [34].

2.2 Antiandrogens

Another method of AAT involves the use of androgen blockades or antagonists such as flutamide and bicalutamide and nilutamide to competitively and directly block the androgen receptors in the cytosol of the prostate cells. These agents are generally used either as intermittent therapy -to prevent the flare phenomenon commonly associated with GnRH agonists or in a monotherapy in patients who prefer this agent to GnRH agonist [35]. The steroidal antiandrogens have been shown to cause inhibition of the secretion of gonadotropins at the level of pituitary, (Fig. 2 and 3) by suppressing the release of LH which results in low testosterone level [14]. In addition, the non-steroidal antiandrogens competitively inhibit the binding of androgens to the androgen receptors with no effects on the LH level; the testosterone level may remain constant and the sexual function may also be preserved [14].
2.2.1 Flutamide

Flutamide was the first non-steroidal antiandrogen agent used in AAT. At the moment, there is paucity of phase III trials using flutamide monotherapy in advanced prostate cancer: however 68% of patients treated with this agent experienced partial response [27]; furthermore, no significant difference was found when its efficacy was compared with DES in a double blind randomised study [36]. This double blind randomised study reported significant side effects like hepatotoxicity, gynecomastia and intolerance to treatment [36].

2.2.2 Nilutamide

A randomised controlled study evaluating the efficacy of Nilutamide in monotherapy was not found at the time of writing this work. However, a comparative study involving only 26 patients found an efficacy of 91% with a median progressive free-survival and median survival duration of 9 and 23 months respectively in patients with advanced prostate cancer [37]. But extrapolating the efficacy of this agent based on this study may result in a mere exaggeration, due to many limitations; including population size, lack of detailed analysis of the end point parameters etc. Furthermore, treatment with nilutamide may be associated with serious adverse effects which may lead to patients withdrawing from studies [37]. Most of the adverse effects are nausea, vomiting, and impotency [27,37].

2.2.3 Bicalutamide (Casodex)

Casodex is the most extensively studied non steroidal antiandrogen agent due to possibly its tolerability. Many studies have evaluated its efficacy in monotherapy for treatment of advanced localised prostate cancer. In a randomised controlled study that examined the efficacy and tolerability of Casodex monotherapy at 150mg daily dose in 1453 patients with either metastatic or non metastatic prostate cancer; [38], found that Casodex significantly improved the objective response by 70% in patients with symptomatic prostate cancer when compared with surgical castration (58%). Further analysis of that study showed that Casodex was associated with improvement in the quality of life, tolerability, and a substantial decrease in adverse reaction. In line with these findings, [39] showed that Casodex at 150mg improved progression free-survival, reduced the risk of objective progression of disease by 44% compared with radiotherapy and reduced the risk of death by 35% compared with radiotherapy. This result has not been confirmed in many clinical studies as poor overall survival and relapse of the cancer are common findings after prolonged therapy [40]. Data from [40] suggest that Casodex at 150mg daily may have significant effects on reducing disease progression at initial phase of treatment of advanced prostate cancer, [40]. The studies further showed an improved quality of life and benefits in tolerability and reduced adverse effects after using Casodex; however there is no current evidence that use of Casodex for treatment of prostate cancer has added any improvement on the overall survival in patients across all published works so far. This creates an opportunity for further works to improve the overall outcome in patients treated with this agent.

2.3 Secondary Androgen Ablation, the Role of Keto Conazole

Ketoconazole is an adrenal androgen synthesis inhibitor. Though used generally as antifungal agent, it is capable of inhibiting cholesterol side chain cleavage enzyme and the 11 beta hydroxylase enzyme that converts progesterone to 17 alpha hydroxyprogesterone, [25]. Multiple phase 1-III randomised controlled trials demonstrated that ketoconazole reduced PSA level; and that it may serve as a potential secondary androgen ablation agent,
following primary antiandrogen withdrawal [25] in patients treated of prostate cancer. Furthermore, the Cancer and Leukaemia group trial 9583 investigated the efficacy of ketoconazole as a single agent and the frequency of antiandrogen withdrawal phenomenon in 260 patients who were randomised to either androgen withdrawal concurrently with ketoconazole or antiandrogen withdrawal, followed by a secondary therapy with ketoconazole. The final result of this study indicated that ketoconazole may be useful; given that the level of PSA was suppressed to as low as 13% in patients treated with ketoconazole after primary androgen ablation; against 30% reduction in PSA (p<.001) in patients that simultaneously withdrew AAT and ketoconazole therapy [25]. The study also buttressed the importance of secondary androgen ablation therapy, even when the castration level of testosterone had been achieved in the primary hormonal ablation.

2.4 Androgen Ablation Therapy and Radiotherapy

Several studies showed conflicting results in the outcomes of interventions involving different modalities of androgen ablation therapy and radiotherapy. [41] reported from a randomised trial of the effect of androgen ablation therapy plus extended beam radiotherapy EBRT in men with localised advanced prostate cancer- that the addition of 4 months androgen ablation therapy to EBRT had impact on meaningful end points. [42], demonstrated that long term androgen ablation therapy plus radiotherapy was superior to short term androgen ablation therapy with radiotherapy in almost all the end point parameters (disease free survival, distant metastasis, local progression, disease specific survival), except overall survival, and suggested that long term androgen ablation therapy with radiotherapy should be the treatment of choice. These findings were corroborated by the result of systematic review of Meta analysis by [43], who reported that long term androgen ablation therapy for 6 to 8 months plus concurrent radiotherapy had survival advantage with significant clinical benefits. [44] recommended long term androgen ablation therapy for up to 2-3 years with concurrent radiotherapy. Unfortunately, this strategy was associated with significant adverse effects. Apparently, there is no available intervention that has a proven effect on the overall survival in patients with advanced prostate cancer. Resistance to androgen ablation therapy in prostate cancer is well documented complication of prostate tumour, and often the leading cause of death in prostate cancer patients. It is therefore necessary to go back to the Laboratory and re-evaluate the changes that lead to the adverse therapeutic effects and decreased overall survival in prostate cancer patients.

2.5 The Changing Paradigm for Androgen Ablation Therapy

2.5.1 CYP17A1 inhibitors (17α-hydroxylase/17, 20 lyase)

As discussed above, decreasing serum testosterone through inhibition of testicular function is the first line of treatment for men with metastatic prostate cancer; however, residual androgens may still be detected in patients treated with luteinizing hormone-releasing hormone agonists or antagonists [45,46]. The cytochrome P450, family 17, subfamily A, polypeptide 1 (CYP17) is essential for synthesis of testosterone from cholesterol. CYP17A1 inhibitor is therefore a selective cytochrome P450 17A1 enzyme inhibitor, recently approved for treatment of hormone refractory prostate cancer [47]. Abiraterone acetate (CB 7630) is an irreversible inhibitor of cytochrome P450–17 (CYP17), with 17α-hydroxylase and C17, 20-lyase inhibitory properties [47]. This drug is often used in combination with prednisolone especially in treating patients with metastatic castration-resistant prostate cancer (CRPC) who have previously received docetaxel-containing chemotherapy [45,47]. This is so
because CYP17 is a key enzyme in the production of androgens and estrogens in the adrenal glands and tumor tissue, therefore both adrenal androgen and intratumoral androgen synthesis are inhibited. However, because of the upstream inhibition of 17α-hydroxylase, the levels of serum cortisol decrease, which can result in positive feedback on adrenocorticotrophic hormone (ACTH) and a risk of hypokalemia and hypertension; these are circumvented by the concomitant administration of dexamethasone or prednisone. In fact, published evidence from clinical studies confirmed that treatment with CYP17A1 inhibitors may result in rapid, and complete, inhibition of androgen synthesis in the adrenal glands and within the tumor [47]. An impressive overall survival benefit of using CYP17A1 inhibitors in achieving maximal androgen ablation was recently demonstrated in a randomized placebo-controlled phase III clinical trial of abiraterone with prednisone versus prednisone in men with metastatic castrate-resistant prostate cancer previously treated with docetaxel chemotherapy [45]. Recently, [48] treated 42 castration-resistant prostate cancer patients with continuous, daily abiraterone acetate and found that abiraterone acetate was associated with accumulation of steroids with mineralocorticoid properties upstream of CYP17A1, which resulted in side effects, including hypertension, hypokalemia, and fluid overload. CYP17A1 inhibition may be characterized by significant suppression of androgen and cortisol synthesis [48]. The latter was associated with a rise in ACTH that causes raised mineralocorticoids, leading to side effects and incomplete 17α-hydroxylase inhibition. Clearly, concomitant inhibition of 17,20-lyase results in diversion of 17α-hydroxyprogesterone metabolites toward androgen synthesis as stated above; this adverse toxicity might be reverted by addition of dexamethasone 0.5mg daily, with further advantage of inducing repression of further androgens synthesis [46,48].

2.5.2 MDV3100 and androgen receptor signaling

It is known that CRPC is often mediated by a gain of function in the androgen receptor (AR), which may occur at the level of androgen receptor (AR) itself or through intratumoral repletion of androgens that in turn stimulate AR [49]. A number of reports in the literature concerning CYP17A1 inhibitors suggest the importance of androgen signalling and androgen receptor signalling inhibitor in patients with castrate-resistant metastatic disease. Current search for better treatment protocol for patients with prostate cancer has resulted in development of other novel agents including the MDV3100; this is a nonsteroidal androgen receptor antagonist. Details of this novel agent is discussed below.

MDV3100 is a nonsteroidal AR antagonist with a greater binding affinity than other AR antagonists currently in clinical use including bicalutamide; but unlike bicalutamide, MDV3100 also inhibits AR function by blocking nuclear translocation and DNA binding and has no agonist activity [45,46]. In a large multicenter phase I and II study done in 140 CRPC patients reported antitumor activity including PSA declines of >50% or more in 78 patients (56%), response in soft tissue in 13 out of 59 patients (22%), and bone disease stabilization in 61 out of 109 patients representing 56% [50]. In that study the circulating tumor cell (CTC) counts were done prospectively: 92% of patients with favorable pretreatment counts (i.e., <5 cells/7.5 mL of blood) maintained favorable post-treatment counts, whereas 49% of patients converted from unfavorable pretreatment (i.e., >5 cells/7.5 mL of blood) to favorable post-treatment counts; the dose of 240 mg/d was defined as the maximum tolerated dose [50]. The most common grade 3-4 adverse event which was reported in the study was dose-dependent fatigue (16% [11%] patients), which generally resolved after dose reduction [50]. Put together, data from the phase 1-2 trial validate preclinical studies implicating sustained androgen-receptor signalling as a driver in CRPC disease.
3. CHALLENGES FOR ANDROGEN ABLATION THERAPY

As stated above, prostate cancer deprived of androgen usually responds to this treatment by decreasing its volume and rate of cell growth; however, the overall consequence of this treatment is a stage where androgen deprivation does not control cell growth. This happens in greater percentage of patients treated with AAT and may be the cause of death in these patients. Large volume of published studies is available which have investigated the androgen resistant treatments in prostate cancer. For example, [51] observed that androgen deprived LNCaP sub lines (LNCap-H1) were fast growing, and had the ability to activate growth of endothelia cells; in addition, these cells were resistant to both chemotherapy and radiotherapy when exposed to radiation. [52] found that the androgen independent prostate cancer cells had decreased apoptosis and acquired higher proliferative rate than the androgen dependent cells. Further studies found androgen receptor gene over-expression and emergence of androgen refractory phenotype following androgen ablation [52,53,54]. Furthermore, gene expression profile of LNCaP cells that were exposed to prolonged AAT in vitro using Casodex showed that membrane metallo endopeptidase, bcl -2, and Cycling G2 which are hypoxia related genes, were over expressed [55]. Also, hypoxia-selected LNCaP sub lines developed androgen independence and were less susceptible to radiation-induced apoptosis and were more tolerant to hypoxia [56]. There are sufficient published studies indicating that treatment with AAT may be associated with severe tumour hypoxia. The molecular role of tumour hypoxia in selecting cells with more malignant phenotype and cells with serious unstable genome has been demonstrated by [56,57]. Currently tumour hypoxia has been identified as a singular promoter of metastatic prostate cancer during AAT. Therefore development of a combined therapy that target tumour hypoxia may significantly improve outcome during AAT in patients with localised prostate cancer.

4. CONCLUSION

Sufficient published evidence has shown that progression in prostate cancer is often mediated by AR signalling, this highlights the importance of subsequent AR targeting after initial androgen ablation therapy. We have provided a detailed review of clinically relevant hormone deprivation protocols for tumor control in prostate cancer. Emerging evidence from phase III study suggests that the CYP17A1 inhibitors, abiraterone acetate, an androgen biosynthesis inhibitor, may take a centre stage in CRPC pre-treated with docetaxel.

An overall survival benefit that has led to approval of this agent for treating CRPC. We have previously reviewed the molecular mechanisms for development of CRPC and highlighted the role of AR signalling [49]. Several agents targeting continued AR signalling have been discussed above including bicalutamide and more novel agents like MDV3100. Data from literature indicate that MDV3100 has a lot of potentials and benefits when compared with other nonsteriodal antiandrogen agents used today. Studies are ongoing to identify potential predictors of response or resistance to AR-signalling targeting agents.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.
COMPETING INTERESTS

Authors have declared that no competing interests exist.

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