Androgen blockade in prostate cancer: a literature review

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ABSTRACT

There is a high prevalence of prostate cancer in Mexico as well as worldwide, mainly affecting older males. Thanks to prostate specific antigen measurements and physical examination, this cancer is being diagnosed at earlier stages in which curative treatments can be offered. However, patients with advanced stage disease are subject to palliative therapy, the aim of which is to diminish disease symptoms and progression. Androgen blockade, whether surgical or pharmacologic, is the cornerstone of this therapeutic intervention and is used according to different modalities and regimens. Pharmacologic androgen blockade involves a wide variety of drugs that have different action mechanisms that include: estrogenic compounds, antiandrogens (steroidal and nonsteroidal), LHRH agonists, LHRH antagonists, and steroidogenesis inhibitors. These pharmacologic groups have advantages and disadvantages in relation to their response, effectiveness, adverse effects, and cost, which will be discussed in this paper. Therefore it is important that prostate cancer treatment be individualized according to each patient's needs. The ongoing research in this area has led to the development of other therapeutic alternatives (immunotherapy and chemotherapy) and new therapeutic targets in the treatment of prostate cancer.

Keywords: Prostate cancer, androgen blockade, hormone-refractory, hormone therapy, Mexico.

RESUMEN

El cáncer de próstata (CaP) tiene una elevada prevalencia en nuestro medio, afectando principalmente a adultos mayores. Gracias a las mediciones del antígeno prostático específico (APE) y a la exploración física, se diagnostica este cáncer en etapas más tempranas ofreciendo tratamientos con fines curativos. Sin embargo, los pacientes con enfermedad avanzada están sujetos a terapia paliativa, cuyo objetivo es disminuir los síntomas y la progresión de la enfermedad. El bloqueo androgénico sea quirúrgico o farmacológico constituye la piedra angular de esta intervención terapéutica, aplicado en sus diferentes modalidades y esquemas. El bloqueo androgénico farmacológico incluye una gran variedad de fármacos que tienen mecanismos de acción diferentes, entre los cuales se incluyen: compuestos estrogénicos, antiandrógenos (esteroideos y no esteroideos), agonistas LH-RH, antagonistas LH-RH e inhibidores de la esteroideogénesis. Estos grupos farmacológicos poseen ventajas y desventajas en cuanto a sus efectos, eficacia, reacciones adversas medicamentosas, así como a su costo a largo plazo. Por lo anterior, es importante que el tratamiento para el CaP sea individualizado de acuerdo a las necesidades de los pacientes. La constante investigación en este tema ha desarrollado otras alternativas terapéuticas (inmunoterapia y quimioterapia), se está trabajando en nuevos blancos terapéuticos en el tratamiento del CaP.

Palabras clave: Cáncer de próstata, bloqueo androgénico, hormono-refractario, México.
INTRODUCTION

Prostate Cancer (PCa) is the most common tumor in men above the age of 50 in the Western world and is a good model for the use of hormone therapy, given that its proliferation is mediated by androgens and its growth is suppressed in their absence. Medical treatment for PCa began with the description of hormonal dependency by Huggings & Hodges which earned them the Nobel Prize in 1941, when they demonstrated that orchectomy reduced the speed of tumor growth.

Testosterone stimulates the androgenic receptors on the prostate cell membrane and is transported inside the epithelial cells where it is converted into dihydrotestosterone by 5-alpha reductase (isotope 1 and 2). Dihydrotestosterone is the most active form of testosterone (30 times greater) and carries out the majority of functions. And so androgen blockade (AB) induces apoptosis in certain susceptible PCa cells by reducing the synthesis of androgens and their interaction with their androgenic receptor.

Once PCa diagnosis is established, the most useful marker for its follow-up and response to AB are the levels of prostate specific antigen (PSA). The risk of death by cancer has been observed to increase when PSA levels are greater than 50 ng/mL at the time of diagnosis, making these patients candidates for AB treatment so that disease progression can be delayed. In contrast, patients with PSA levels that are lower than 8 ng/mL at diagnosis are at low risk for death by cancer when they undergo therapy with a curative intent.

ANDROGEN BLOCKADE

Androgen blockade (AB) is the cornerstone of treatment for metastatic PCa because it increases overall patient survival and delays disease progression and the appearance of symptoms. It is also employed as an adjuvant in therapies with curative intent such as external beam radiotherapy and brachytherapy in high risk localized disease and in locally advanced PCa; the purpose of this is to make cancer cells more susceptible, and in some cases it is administered as a preparation for patients that are candidates for radical prostatectomy, in an effort to reduce tumor volume and increase the possibility of negative surgical margins.

PHARMACOLOGIC AB INDICATIONS AND MODALITIES

There is a wide variety of effective drugs for achieving testosterone levels lower than those attained with castration, and this is why AB plays an important role in advanced PCa treatment. AB treatment is not innocuous, and because of the side effects involved, it is important to consider the length of time AB will be administered and the type of medication chosen in order to individualize each treatment according to complications, risks, and costs, among other factors.

1) Neoadjuvant hormone therapy. The time to start AB is proposed prior to a curative treatment (surgery or radiotherapy) in order to reduce tumor size, to improve outcome, and to reduce the adverse effects and complications of the procedure used. It has been associated with an increase in disease-free survival and a better local control in both modalities. However, it has also been argued that there are no advantages in relation to overall survival and disease control in localized stages.

In the case of radical prostatectomy, the pathologist must consider the morphological changes induced in the surgical specimen due to the hormonal deficiency in the tumor. These changes can make the evaluation of the surgical margins and capsular invasion difficult. Therefore, guidelines such as the NICE from the United Kingdom recommend administering AB at least 3 to 6 months before curative therapy. The Canadian Uro-Oncology Group specifically recommends its use up to 8 months prior to radiotherapy.

2) Adjuvant hormone therapy. Adjuvant hormone therapy is indicated for locally advanced PCa that is managed with external beam radiotherapy with a curative intent. Studies such as the RTOG 85-31 and the EORTC 22863 showed an improvement in overall survival and in PCa-specific mortality. The duration of AB as adjuvant treatment in addition to radiotherapy is variable and can last up to 2 to 3 years after the radiations are finished.

Adjuvant hormone therapy is indicated in patients that are candidates for radical prostatectomy and that had positive pelvic lymph nodes or locally advanced disease, according to the European guidelines. Different meta-analyses have shown an increase in 5-year overall survival, in disease-free survival, and in local control in 80% of patients, emphasizing survival in PCa patients with macroscopic lymph node involvement.

AB REGIMENS

AB administration varies in relation to the length of prescription time and to the approach used and depending on whether the effect is at the central or the peripheral level, it is subdivided into:

- Total AB (TAB): has been available since 1989 and its aim is to block adrenal androgen production or its effect at the peripheral level. It is indicated in...
pharmacologic (with LHRH agonists) or surgical castration. It increases survival by 5%, compared with LHRH agonists used in monotherapy. In patients with metastasis, drugs that have central action at the hypothalamic-pituitary-adrenal (HPA) axis are mainly used. Together with nonsteroidal antiandrogens, they block target organ androgen production (the testes and adrenal glands), abolishing the effect of testosterone by 100%. Their disadvantages are the adverse effects of androgen deficiency (erectile dysfunction, low bone mineral density, cognitive alterations, thermoregulatory dysfunction, etc.).

• Partial AB (PAB): involves drugs that inhibit testicular androgen production (70-85%) are used in PAB and do not block adrenal androgen production or action and so the patient maintains a certain hormonal stimulus that could cause faster disease progression. Some studies report a progression similar to TAB, with the advantage of less intense low testosterone symptoms.

• Continuous AB (CAB): is administered uninterruptedly starting at the time of diagnosis, during disease progression, and until the patient reaches a hormone-refractory state or dies.

• Intermittent AB (IAB): is implemented in periods of androgen deficiency followed by phases with no treatment (holiday), depending on the time to progression. It is defined by periodical measurements of PSA, serum testosterone, and clinical manifestations (every 3 to 6 months). The main aim of IAB modality is to reduce the undesirable effects of CAB through periods of non-treatment during which there is an increase in testosterone, allowing for a temporary improvement in: quality of life, erectile function, in muscle mass, strength, and mood changes. Bone demineralization is reduced, there is a reduction in costs, better treatment adherence, and a delay in the transition to a hormone-refractory state (which appears with CAB in 18 to 30 months on average). An important aspect of IAB benefits is that oncologic effectiveness is similar to CAB, according to the European Urological Association 2010 guidelines.

There should be an induction period with CAB lasting for at least 6 to 9 months, before initiating IAB. According to the literature, the most widely accepted moment to restart AB therapy is when there is an increase in the PSA above 4 ng/mL (4-15 ng/mL range) in non-metastatic disease and over 10 (10-20 ng/mL range) in metastatic disease. It is important to emphasize that patients with extensive metastatic disease are not good candidates for IAB due to their rapid disease progression.

The addition of 5-alpha reductase inhibitors, such as finasteride or dutasteride (drugs used in the treatment of benign prostatic hyperplasia), has recently been proposed for blocking the conversion of testosterone into dihydrotestosterone with fewer adverse effects, if compared with AB in the non-treatment period, and this could prolong the period of time without AB as long as possible.

**SURGICAL BLOCKADE**

AB began with simple bilateral orchiectomy in 1941, by a scrotal incision, with pulpectomy (sparing the epididymis and the spermatic cord to have some residual tissue to diminish the sensation of scrotal emptiness) or total testicular parenchymal resection at the distal cord. It has the benefits of being an immediate treatment (testosterone levels near 0.2 ng/mL are observed 8 hours after surgery) that improves survival and slows down disease progression. It has a lower cost than prolonged pharmacologic AB and can be performed as an out-patient procedure with local or regional anesthesia. However, its limitations are:

1. Persistence of adrenal androgen production (15-20% of the total serum testosterone production), resulting in a PAB.
2. Its irreversibility does not allow for the possibility of IAB.
3. It is not useful in cases of castration-resistant or hormone-refractory PCa.
4. It is a surgical procedure and as such involves a low risk for complications (infection, anesthesia-related problems, hematoma, among others).
5. Some patients suffer from chronic pain related to the procedure itself (more frequently found with pulpectomy).
6. It has a psychological impact on patients with certain social prejudices.

**AVAILABLE DRUGS FOR HORMONE THERAPY OR AB**

Today there are distinct pharmacologic options for suppressing testosterone to castration levels in managing PCa patients. These include estrogen derivatives, steroidal and non-steroidal antiandrogens, LHRH analogs, and LHRH antagonists.

**Estrogens.** Historically, stilbestrol derivatives were the first hormonal treatment therapies described for PCa. Diethyl stilbestrol (DES) has a suppressing effect on LHRH release from the hypothalamus, on gonadotropins from
the pituitary gland (LH and FSH), and on testosterone from the testes by means of negative feedback. They possess an added cytotoxic effect on tumor cells that is involved in the reduction of intratumoral androgen (the compound dephosphorylates and the free stilbestrol induces apoptosis).  

Dose can vary from 1 to 5 mg every 24 hours. However, the recommended dose with the fewest adverse effects is 2 mg every 24 hours. Oral administration is absorbed well, reaching plasmatic testosterone levels of 0.2 to 0.8 ng/mL, depending on the dose within the first 30 days of its administration. Adverse effects are dose-dependent and the greatest adverse effect is cardiovascular prothrombotic risk (arterial and venous thrombosis). Other lesser adverse effects include gastrointestinal disorders (nausea, vomiting), water retention, erectile dysfunction, gynecomastia, lipid profile alteration, and metabolic syndrome. Patients with liver failure have more adverse effects due to its hepatic metabolism. Nowadays estrogen use has diminished (it is currently not considered part of first-line therapy) because of its prothrombotic effect and the availability of other drugs with a safer pharmacologic profile, and it is currently used only in very well selected patients because of its high risk for cardiovascular mortality. However, there are reports that state that the thrombotic complications can be almost completely reduced to levels similar to those for the general population if it is taken simultaneously with acetylsalicylic acid (100mg) (apparently warfarin does not reduce cardiovascular risk).  

Another benefit of the estrogen derivatives is their low cost. Their effect is similar to that of orchietomy in relation to the reduction of disease progression and to greater survival, and so the use of these drugs depends on the morbidity associated with estrogenic adverse effects. Their combined use (orchietomy and estrogens) is not recommended because it is not superior to the monotherapeutic use of each one of them. There are studies that show there is no difference in tumor progression between DES and flutamide. However, there is greater survival with DES, but more adverse events. It has been proposed as a second-line AB therapy because estrogen derivatives are useful in treating castration-resistant PCa, reducing autonomous androgen synthesis mediated by its cytotoxic effects, and causing lower PSA levels in 43% of patients when it is administered in low doses.

**Antiandrogens.** They function by blocking the binding of natural androgens with their receptors through competitive antagonism, taking its place in the androgen receptor and consequently preventing effector cell activation. This gives them an important short-term role when LHRH agonist therapy is started because they prevent the flare-up effect produced by the peak in testosterone secretion. They are classified in relation to their mechanisms of action as follows:

a. **Steroidal antiandrogens:** these are drugs that belong to the progestin group and have a double effect: at the peripheral level they interfere with androgen receptor activation and at the central level they have a progestational effect, given that they impede gonadotropin secretion through negative feedback, which results in the reduction of plasmatic testosterone levels.  

b. **Non-steroidal antiandrogens:** they cause fewer adverse reactions due to their chemical properties, which has earned them the name of pure antiandrogens, because they lack progestational action and their effect is limited to the androgen receptor (19). Greater increases in survival have been obtained when they are administered as part of TAB in addition to LHRH analogs. The drugs that make up this group have a similar biochemical structure and they include:

- **Flutamide:** the recommended dose is from 375 to 750 mg every 24 hours and preferably every 8 hours because its bioavailability is short (5-8 hours,

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Flutamide monotherapy has response rates depending on age.\textsuperscript{1,18,19,38} After its effective absorption in the digestive tract, hepatic metabolism transforms it into 2-hydroxyflutamide, which is the active metabolite that blocks dihydrotestosterone binding at androgen receptors, reaching serum testosterone levels of around 6.64 ng/mL at 12 weeks.\textsuperscript{19}

Gastrointestinal adverse effects stand out and are characterized by nausea, vomiting, and diarrhea. Other adverse effects include gynecomastia, galactorrhea and hepatotoxicity. Less common are anemia, leukopenia, thrombocytopenia, myocardial infarction, and high blood pressure.\textsuperscript{1,19} There is a lower incidence of gynecomastia and galactorrhea when flutamide is administered together with LHRH analogs (9% vs 34-42% in monotherapy).\textsuperscript{19}

Flutamide monotherapy has response rates comparable to DES in relation to tumor progression, but it is not superior to surgical castration.\textsuperscript{1} It has similar results to those seen with cyproterone, but its toxicity is more significant and there is a decrease in erectile function and sexual drive of the patients.\textsuperscript{36} Nevertheless, comparative analyses on sexual function (presence of spontaneous diurnal/nocturnal erections, sexual activity, erections resulting from sexual excitement, orgasms) have shown that the decrease in this function is progressive and slower than with orchietomy (50% of the patients treated with cyproterone or flutamide are functional the first year), making them advantageous for improving functional prognosis and quality of life if they are administered intermittently.\textsuperscript{39} Flutamide monotherapy is not superior to TAB because flutamide plus LHRH agonists increases disease-free survival and overall survival.\textsuperscript{1} Its use together with bilateral orchietomy in metastatic disease has not been able to increase survival, as shown in a study by Eisenberger et al. in which they compared 700 patients treated with flutamide at a dose of 750 mg plus bilateral orchietomy vs 687 patients treated with bilateral orchietomy plus placebo.\textsuperscript{40} Its suspension as second-line hormonal treatment in castration-resistant PCa has also been shown to be useful, providing a partial short-term clinical improvement with 50% decreases in PSA in up to 40% of patients for a 4 to 6-month period (flutamide withdrawal syndrome).\textsuperscript{1,8}

- Nilutamide: shares the mechanism of action of flutamide and has similar chemical properties, but it has the advantage of having a longer half-life (30-60 hours) after its adequate absorption in the digestive tract, as well as prolonged hepatic metabolism, and therefore its recommended dose is 150-300 mg administered once a day.\textsuperscript{19,41}

- Its adverse effects are similar to those of flutamide, but the ones that stand out are interstitial pneumonitis, visual abnormalities (especially night vision), high blood pressure, and an antabuse effect, thus limiting its use in patients with hepatic disease and respiratory insufficiency. The hepatic adverse events are usually observed after 4 months of treatment.\textsuperscript{41} Despite the fact that this drug has been associated with severe side effects, a study that included 457 patients that were in treatment for advanced stage disease showed that the combination of nilutamide with orchietomy, during an 8.5-year follow-up, was well tolerated. No increase in the incidence of drug-specific adverse events was observed, and there was a significant survival increase.\textsuperscript{42} Because it is a drug that has a higher incidence of adverse events in comparison with the other non-steroidal antiandrogens, its use has been greatly limited.\textsuperscript{33}

A meta-analysis that evaluated the results of seven double-blind randomized studies on 1056 patients with stage D PCa\textsuperscript{41,44} showed that nilutamide plus orchietomy reduced disease progression, metastatic symptoms (especially bone pain), and prostatic acid phosphatase and alkaline phosphatase levels. The Anandron International Study Group demonstrated that this therapeutic combination is superior, specifically in relation to disease progression and bone symptoms, compared with orchietomy as a monotherapy.\textsuperscript{45} The results obtained by this study group and the Italian Prostatic Cancer Project concluded that disease-free survival in metastatic PCa patients treated with nilutamide monotherapy was 9 months on average, compared with 14.7 months in patients that underwent orchietomy alone, and 20.8 months in those treated with nilutamide plus orchietomy.\textsuperscript{45,46}

- Bicalutamide: This drug has an affinity for the androgen receptor that is four times greater than that of flutamide. It has a half-life of approximately six to seven days, longer than that of nilutamide, and can be given in oral doses of 50 to 150 mg once a day, with good but slow gastrointestinal absorption.\textsuperscript{1,18,19} It can be used as combined therapy, as monotherapy, or as adjuvant therapy at a dose of 150 mg/day. It is described as the strongest nonsteroidal antiandrogen drug.\textsuperscript{19}

The most important adverse effects of bicalutamide are mastitis and gynecomastia and they can be present in up to 62% of the patients, but it stands out for being less toxic.\textsuperscript{19} Gastrointestinal effects (mainly diarrhea) are less intense. It does not significantly affect sexual function (lower frequency of erectile dysfunction and decreased libido), it causes less muscle mass loss, less fatigue, better bone mass density, and physical capacity is maintained and quality of life is improved, all of which results in better treatment adherence and tolerance.\textsuperscript{19} The positive effect on bone mineralization ·
was shown in a study carried out by Smith MR et al. in which an increase in bone density was observed in 2.5% of the patients from the baseline after 12 months of drug administration.16,17 Bicalutamide monotherapy is an excellent alternative in localized disease and its effect is even stronger if it is combined with radiotherapy in locally advanced stages.47 Tumor progression is reduced, but overall survival is not increased as shown in a study carried out by the Early Prostate Cancer Program with a 7.4-year follow-up, in which the use of bicalutamide plus standard treatment (radical prostatectomy or radiotherapy) compared with standard treatment alone, was analyzed.16,48 Different studies have shown that bicalutamide monotherapy at a dose of 150mg/day in locally advanced and metastatic disease is not superior in relation to overall survival compared with orchiectomy. However, it has the advantage of causing a lower incidence of hot flashes, along with greater libido and physical capacity, and so is proposed as a treatment of choice in metastatic PCA patients in whom surgical castration is contraindicated.49-50 Bicalutamide employed in TAB together with LHRH agonists reduces tumor progression, increases the length of time until hormone resistance, and improves overall survival more effectively than monotherapy with LHRH agonists in metastatic or locally advanced disease.51 Thanks to its low adverse effect rate, its use together with LHRH analogs is superior to flutamide in TAB and causes fewer gastrointestinal alterations, but its effects in relation to survival and disease progression duration are similar.52 It is also useful as second-line therapy in non-metastatic castration-resistant PCa, reducing PSA in close to 50% of patients for a mean length of time of 1.5 years, and increasing metastasis-free survival.53

**LHRH agonists.** The main characteristic of LHRH agonists is their action at the central level (HPA axis). They exert their effect by means of a negative regulation of the quantity of receptors for LHRH after a period of continuous administration, suppress LH, testosterone, estrogen, and plasmatic alkaline phosphatase secretion, through a desensitizing process.19 It is important to take into account the fact that there is a temporary peak in the secretion of LH, testosterone, acid phosphatase, and PSA in the first two or three weeks of treatment, increasing the clinical manifestations and the risk for complications secondary to PCA growth or to metastases (flare-up effect), such as urethral obstruction, pain, pathologic fractures, and medullary compression.16 In order to avoid this acute progression, antiandrogen compounds should be started at least one month before starting a LHRH analog treatment.54 An advantage of LHRH agonists is that they can be administered intermittently.27 They are able to reach androgen levels similar to those obtained with surgical castration (0.2-0.5 ng/mL around the third and fourth weeks) making them a good alternative to bilateral orchiectomy, with a similar 2-year overall survival effect.19,48 Parenteral depot presentations are available that can be applied monthly or every two, three, six, and 12 months, providing greater comfort for the patient by reducing the number of medical visits and increasing treatment compliance.1 The currently available analogs include: leuprolide, goserelin, histrelin, triptorelin, and buserelin.

— **Leuprolide:** This drug is a synthetic LHRH analog that is subcutaneously administered and is 15 to 20 times stronger than endogenous LHRH.55 It can be used once a month at a dose of 7.5 mg, every three months at a dose of 22.5 mg, every 6 months at a dose of 45 mg, and every 12 months at a dose of 65 mg as a subcutaneous implant. It reduces testosterone levels to castration levels in 2 to 5 weeks in 100% of patients with no increases between following applications.55,56 The most notable adverse reactions are hot flashes, fatigue, testicular atrophy, gynecomastia, and nausea. Local application can be accompanied with transitory pain, erythema, pruritus, and hardening at the insertion site.55 The negative effect on bone mineralization is greater than that with the use of antiandrogens, such as bicalutamide.19 The dose of leuprolide every six months has achieved an effect comparable with that of bilateral orchiectomy. At the end of 12 months, a study that enrolled 1273 patients showed mean PSA values of 0.5 ng/dL and mean testosterone values of 8.9 ng/dL.55 Its effect on the levels of testosterone, dihydrotestosterone, acid phosphatase, and one-year survival at a dose of 1 mg/day was similar to that of DES administration at a dose of 3 mg/day, but with fewer adverse effects.58 Another study comparing leuprolide with goserelin concluded that their effectiveness was comparable, reaching testosterome levels below 0.5ng/mL.59 Leuprolide combined with flutamide in TAB produced a greater increase on overall survival and on progression-free survival when compared with its monotherapeutic use (35 vs 27.9 months and 16.9 vs 13.9 months, respectively).40,60 Leuprolide plus an antiandrogen (flutamide or bicalutamide), when compared with goserelin plus an antiandrogen had similar effects concerning survival and disease progression duration.61 The Lupron Depot Neoadjuvant Prostate Cancer Study Group22,63 initially reported that leuprolide administered 3 months before surgery together with cyproterone acetate or flutamide, reduced tumor size and positive surgical margin.
Adverse reactions are similar to those of AB, as well as —

Studies by Bolla et al. and the RTOG 8531 have shown that the most important adverse events are hyperhidrosis, tumor progression, (statistically significant p=0.016).68,69 Superior to cyproterone acetate monotherapy in regard to treatment resources after 4 weeks of use. However, it was testosterone were reduced to castration levels with both testosteron et al. and liver or renal insufficiency and does not need dose adjustments. 66

Studies by Bolla et al. and the RTOG 8531 have shown that caudal goserrin administration during radiotherapy improved local disease control as well as 5-year survival (79% vs 62%) 66,67 and its effectiveness was comparable with that of orchietomy in relation to survival. The levels of acid phosphatase, alkaline phosphatase, and plasmatic testosterone were reduced to castration levels with both treatment resources after 4 weeks of use. However, it was superior to cyproterone acetate monotherapy in regard to tumor progression, (statistically significant p=0.016).68,69 Both goserrin and DES have the advantage of causing fewer adverse effects and having a positive impact on quality of life 68,70. Despite the fact that the effects of leuprolide or goserrin plus bicalutamide or flutamide in TAB are similar, with comparable survival and tumor progression results, the specific combination of goserrin plus flutamide is superior to orchietomy, as was shown in the EORTC 30853 study.61,71 The combination of goserrin plus DES, cyproterone acetate, or flutamide in the TAB has no advantage over goserrin monotherapy in relation to tumor progression and survival but it does have the advantage of reducing the side effects from androgen deficiency on thermoregulation and it avoids the flare-up effect.69,72,73

— Triptorelin: This synthetic LHRH agonist is administered intramuscularly at a monthly dose of 3.75 mg, 11.25 mg every three months, and of 22.5 mg every six months, resulting in continuous testosterone reductions to castration levels starting from 2 to 4 weeks after application, with these results in 92.7 to 97.7% of advanced PCa patients receiving these different doses in non-comparative studies.74,75 Adverse reactions are similar to those of AB, as well as those associated with flare-up (bone pain and urethral obstruction). Reactions at the injection site occur in 6.7% of the patients. Although its metabolism and excretion are hepatic and renal, it also has the advantage of not needing dosage adjustments in patients with kidney or liver failure. 75

This drug is indicated in patients with metastatic and locally advanced PCa and provides similar results to those of orchietomy in relation to PCa-specific survival.76 A comparative study of 284 patients with advanced disease showed that triptorelin had the same effect on testosterone suppression as leuprolide, and a superior effect on 9-month survival.77 Although testosterone elevations between applications have been observed in 3.3% of the patients undergoing triptorelin treatment, studies registered with the FDA show that this drug is superior to leuprolide in maintaining stable testosterone levels throughout the entire treatment.75,78,79 Neoadjuvant triptorelin therapy together with surgery (radical prostatectomy) does not increase survival. However, when it is employed as a neoadjuvant AB with radiotherapy, not only does it reduce tumor size, but it shows a positive survival effect in patients with a Gleason score of 2 to 6.79

— Histrelin: is another subcutaneous implant that is administered annually. Of all the LHRH agonists, it is the most potent and is 1.5 times stronger than goserrin and 10 times stronger than leuprolide. The implant contains a dose of 50 mg and releases 50 µg/day.70,81 Testosterone levels similar to those with castration are achieved within four weeks from the time of implant insertion and this effect lasts for 52 weeks. Testosterone flare-up has not been observed (levels are maintained under 20ng/dL) and PSA levels begin to decrease significantly at week two, with PSA baseline level reductions of 90% at week 16.80,82 When the implant is removed, reversibility of the effect on testosterone and LH occurs within three to nine weeks and one to six weeks, respectively. This time lapse is shorter compared with those reported for buserelin and goserrin (up to nine months).83 The adverse effects most commonly associated with AB and that present most frequently are thermoregulation abnormalities (24.1%), implant site reactions such as a burning sensation or pain (3.9%), as well as fatigue, testicular atrophy, and gynecomastia. 56 One case of hepatic lesion related to implant use has been reported.84 The advantages of this drug include greater comfort for the patient with respect to treatment adherence, fewer required visits to the physician for drug application, lasting and reliable testosterone suppression for up to 4.5 years with no temporary elevations, and no flare-up effect from repeated drug administration.60

LHRH antagonists. These drugs cause a rapid decrease in serum levels of LH, FSH, and testosterone through their direct binding with LHRH receptors, competing with endogenous LHRH without
producing receptor activation and consequently avoiding the flare-up effect that presents with LHRH analog administration. The drugs used in this group are abarelix and degarelix.

— **Abarelix:** This drug is administered intramuscularly at a dose of 100 mg in its depot presentation. Testosterone levels below 50 ng/dl are achieved in 94% of patients on day 29 after its administration. However, its effectiveness is reduced with repeated drug administration and the percentage of patients with castration levels of testosterone gradually decreases.86

The main adverse effects are hypersensitivity reactions (1.1%) (skin rash, pruritus), hypotension, and syncope. They occur at the beginning of treatment (from the first half hour of administration) and the risk for recurrence increases proportionally to treatment duration. These hypersensitivity reactions are caused by the increase in histamine secretion due to the fact that all LHRH antagonists stimulate mast cells. Other adverse effects are QT-segment prolongation, hepatic enzyme increase, sleep abnormalities, vertigo, headache, chest pain, back pain, and constipation, along with the common AB symptoms.85

Abarelix has the advantage of causing pharmacologic castration more rapidly without being associated with testosterone flare-up after its administration, guaranteeing the avoidance of secondary metastatic symptoms in 100% of the patients. Specific indications include symptomatic metastatic cancer and patients that are not candidates for receiving treatment with LHRH analogs due to risk for spinal cord compression, urethral obstruction, analgesic-resistant metastatic bone pain, patients that do not accept surgical castration, and PCa patients that have no other treatment option.85,86 A randomized phase III study that included 269 patients evaluated the effectiveness of abarelix against leuprolide monotherapy and showed that castration levels of testosterone were reached in 78% and 0% of patients, respectively, on the seventh treatment day, with no flare-up effect.86 This same rapid decrease in testosterone levels was observed in the comparison of abarelix with leuprolide combined with bicalutamide in TAB, and no differences in PSA level decreases or in the maintenance of testosterone levels under 50 ng/dl throughout the treatment with any of these therapeutic resources were observed.87

— **Degarelix:** this option is subcutaneously administered deep into the abdominal wall at an initial dose of 240 mg (in two syringes of 120 mg each, for simultaneous bilateral application) the first month, followed by 80 mg monthly doses.86-91 It suppresses testosterone levels under castration levels in 96% of patients from day three of its administration (52% reach it the first day). A 12-month study on degarelix effectiveness and safety showed that 97.2% of the patients maintained testosterone levels below 50 ng/mL throughout the study.92

Adverse events of degarelix are associated with those of AB, such as pain and erythema at the drug application site, hepatic enzyme level elevation, an increase in body weight, and an interesting reduction in the incidence of hot flashes. However, its main advantages are the speed with which testosterone and PSA levels are reduced, the absence of allergic reactions caused by histamine release that presents with other LHRH antagonists, the absence of the flare-up effect produced with LHRH analogs, and the maintained suppression of testosterone during drug administration.93,94

Degarelix is indicated as a palliative medication in advanced stage PCas with a risk for complications secondary to the testosterone flare-up effect (including spinal cord compression, urethral obstruction, or bone pain) and in patients with biochemical recurrence after interventions of curative intent.95 The effects of degarelix are comparable with those of leuprolide according to the CS21 study, because both drugs are able to reduce testosterone to castration levels, however, both testosterone and PSA levels are reduced in a shorter period of time with degarelix.92 It showed a lower risk for biochemical failure (PSA) and death, but even though significant early reduction in PSA and testosterone levels have been observed, its use is not associated with an increase in overall survival.93 Degarelix reduced alkaline phosphatase to lower levels when compared with leuprolide and so it has been suggested that it could provide better bone metastasis control.94 In the extension of the CS21 (CS21A) study, patients that switched from leuprolide to degarelix treatment were seen to show results similar to those in patients that had initially been in treatment with degarelix, having lower PSA level progression and skeletal muscle adverse effects. Therefore it was concluded that degarelix is a drug that can be considered as a first-line therapeutic resource in androgen deprivation.89

**Steroidogenesis inhibitors.** This drug group forms part of second-line hormonal therapy and interferes with androgen synthesis in the adrenal glands by inhibiting the P450 cytochrome, limiting the enzymatic reactions of steroidal compound hydrolysis at different levels.1 The main compounds of this group are ketoconazole and aminogluthimide.

— **Ketoconazole:** This drug is an imidazole that has useful properties for treating certain mycoses, and it has also been used to decrease androgen levels in PCa.
through the administration of a 200 to 400 mg oral dose every 8 hours. It needs stomach acid in order to be adequately absorbed. Its administration at High Dose Ketoconazole can suppress androgen levels by 90% within 48 hours. Allan Pont et al. observed that patients treated with ketoconazole at doses of 200, 400, and 600 mg had a marked reduction in testosterone levels that returned to normal within 8 to 24 hours after stopping the drug, once the blood concentration levels of ketoconazole decreased.

The side effects of this drug are mainly dose-dependent and have the advantage of being totally reversible. Adrenal insufficiency secondary to ketoconazole administration is one of its main adverse effects, making it necessary in some cases to consider steroid replacement. Ketoconazole is metabolized in the liver with an important risk for hepatotoxicity, causing hepatic enzyme abnormalities and inhibiting the metabolism of several drugs. Other frequent adverse events are gastrointestinal disorders (nausea and vomiting in 27% of the patients, as well as abdominal pain) and skin rash. There is evidence that its use at a low dose (200 mg three times a day) provides the same benefits without increasing the incidence of adverse reactions.

This drug has shown its usefulness mainly as second-line hormonal therapy specifically in the treatment of castration-resistant PCa. A study with 78 patients demonstrated a 75% reduction of PSA levels in 44% of the patients, and another study reported a reduction greater than 50% in 40 to 63% of the patients with high dose ketoconazole (400 mg three times a day). However, as previously mentioned, ketoconazole use is recommended at lower doses due to its high incidence of hepatotoxicity. Pont et al. and Trachenberg showed that its administration resulted in better bone pain control in metastatic disease, while in another study with 60 participants, Scholz and Strum concluded that its use in patients with a PSA under 10 ng/dL obtained therapeutic responses for a longer period of time than patients with a higher PSA (25 months vs 4 months, respectively). The CALGB 9583 study demonstrated that ketoconazole used together with antiandrogen withdrawal as secondary hormonal manipulation was superior to AB suspension alone in reference to PSA levels, but it did not show an increase in overall survival.

Aminoglutethimide: This drug was originally designed for epilepsy, but it had the adverse event of adrenal insufficiency, making it a treatment option for Cushing's syndrome and advanced PCa. At an oral dose of 1 to 1.75 g every 24 hours, adrenal suppression is reversed 72 hours after drug suspension. Like ketoconazole, aminoglutethimide causes adrenal insufficiency, requiring hormone replacement treatment with hydrocortisone. Another common adverse effect is orthostatic hypotension due to vascular volume deficiency secondary to a decrease in mineralocorticoid production. Finally, other adverse events are nausea, hypothyroidism, fatigue, dizziness, ataxia, and dermatitis.

It is used as second-line hormonal treatment in advanced castration-resistant PCa. Aminoglutethimide plus hydrocortisone reduces PSA baseline levels by up to 50% in 48 to 65% of patients. A comparative study of aminoglutethimide plus hydrocortisone and medroxyprogesterone plus hydrocortisone in 59 patients with castration-resistant PCa showed better results with aminoglutethimide plus hydrocortisone in relation to objective responses and symptom improvement (31% vs 5% of the patients). Sartor et al. discovered the effectiveness in the use of aminoglutethimide combined with flutamide withdrawal in which baseline PSA levels were reduced by 80% in 48% of the patients, while in another similar study, Dupont et al. reported a 75% patient response.

Other Therapies

Immunotherapy: Dendritic cells: Dendritic cells belong to innate immunity and the most efficient antigen presenting cells, whose purpose is to carry out the presentation of antigens to the T and B lymphocytes, both virgin and memory, to later trigger a specific immune response. Thus in tumor diseases such as PCa, they have the capacity to detect specific immunogenic fragments of those neoplastic cells, causing activation of T CD8+ cytotoxic and CD4+ helper lymphocytes that eliminate neoplastic cells and reinforce cellular immunity/antigen presentation, respectively through different ligands and chemical mediators.

The use of this immunologic therapy is carried out through vaccines that contain autologous dendritic cells that are sensitized or bonded to immunogenic protein fragments belonging to the tumor cell strain (epitopes) that are restricted to HLA A2 or that are transfected with RNA sequences that encode for a certain antigen. This causes T lymphocyte activation after antigen presentation and the carrying out of its effector activities, when administered parenterally to the patients. These cells are obtained from centrifuging peripheral blood of the patient in whom monocytes are isolated, to be differentiated to dendritic cells when GM-CSF and IL-4 are administered, to then later expose them to the antigen (obtained by lysing the tumor cells or through transfection of amplified RNA sequences) for their processing and binding to the molecules.
of the major histocompatibility complex, in order to allow for the antigen presentation.\textsuperscript{110,111}

There are different protein products that are employed as epitopes for immunologic therapy (PSA, prostate specific membrane antigen [PSMA], prostatic acid phosphatase, human telomerase reverse transcriptase, prostate stem cell antigen, transient receptor potential melastatin 8, and surviving). However, they need dendritic cells to increase the immune response, because even though dendritic cells have been identified in normal prostate tissue, and are considerably elevated in neoplastic prostates, they need to be reinforced and administered parenterally to induce the immune response.\textsuperscript{107,110,112}

In 2010 the FDA approved the use of vaccines of dendritic cells, sensitized with a fusion protein (PA 2024), containing colony-stimulating factor of granulocytes-macrophages and prostatic acid phosphatase for the treatment of asymptomatic, or mildly symptomatic, metastatic hormone-refractory PCa. The vaccines are applied intravenously every two weeks in three doses.\textsuperscript{107,113} Prostatic acid phosphatase is found in 95\% of prostate tumors and is highly specific for this tumor tissue and thus has been considered to be the best available antigen for vaccine production and immunologic response in these patients.\textsuperscript{108} Small et al. conducted phase I and II sequential clinical studies to determine the safety and effectiveness of this treatment and they reported that the vaccine produced an immunologic response in 38\% of the patients compared with prostatic alkaline phosphatase, with over 50\% reductions in PSA levels in three patients and from 25 to 49\% in three other patients. The most frequent adverse events were fever (in 14.7\% of the patients)\textsuperscript{111} and local application reactions.\textsuperscript{108} Phase III studies such as the D9901, D9902A, and IMPACT studies were later carried out concluding that this resource has a positive effect on overall survival compared with a placebo (25.9 months vs 21.4 months, 23.2 months vs 18.9 months, 25.8 months vs 21.7 months, respectively), making it another available treatment option for hormone-resistant PCa before chemotherapy, because it needs an intact immune system.\textsuperscript{107}

\textbf{Chemotherapy:} Chemotherapy is indicated for PCa as rescue/palliative treatment in patients with metastatic symptoms in whom tumor tissue has ceased to respond to both first-line and second-line hormone deprivation therapy, in other words, when AB treatment has become hormone-refractory.\textsuperscript{114} In the past, compounds such as estramustine, cisplatin, cyclophosphamide, vinblastine, vinorelbine, and mitoxantrone were used without achieving a survival increase. However, for approximately three decades, another group of chemotherapy agents has been available, that belongs to the taxane group. These include paclitaxel and docetaxel, and they have been shown to provide superior benefits when compared with other compounds. They have mainly substituted mitoxantrone, which had been considered the standard treatment for hormone-refractory PCa since 1996.\textsuperscript{33}

After its approval by the FDA as hormone-refractory PCa treatment, mitoxantrone was administered at a low dose of 12 mg/m2 with prednisone 10 mg/day, achieving significant benefit in bone pain control. It was also superior to prednisone (or hydrocortisone) monotherapy according to various clinical studies, among them the CALGB9182. However, it was not successful in having any benefit on overall survival.\textsuperscript{33,114,115}

Docetaxel is currently considered to be the first-line chemotherapeutic agent in hormone-refractory PCa.\textsuperscript{116} The proposed mechanism of action is the induction of apoptosis in tumor cells by means of phosphorylation of the anti-apoptotic protein Bcl-2, as well as its bonding to microtubules during cell division, blocking their depolymerization.\textsuperscript{117,118} The dose used is of 75 mg/m2 every three weeks plus 10 mg/day of prednisone.\textsuperscript{118} Its reported adverse events are neutropenia, fatigue, nausea, vomiting, diarrhea, epistaxis, sensory neuropathy, alopecia, and unglue changes.\textsuperscript{117,119}

Its approval as first-line chemotherapy treatment came after two phase III studies, the SWOG 9916 and the TAX 327.\textsuperscript{33} The TAX 327 is a study that enrolled 1006 patients comparing docetaxel plus prednisone results with those of mitoxantrone plus prednisone. Docetaxel plus prednisone administered every three weeks was found to have better survival rates (18.9 months vs 16.5 months), a decrease in baseline PSA levels equal to or greater than 50\% (45\% vs 32\% of the patients), and an improvement in bone pain control (35\% vs 22\% of the patients).\textsuperscript{119} The SWOG 9916 study included 674 patients and compared the administration of docetaxel plus estramustine with that of mitoxantrone plus prednisone. The group treated with docetaxel plus estramustine had a higher overall survival rate (17.5 months vs 15.6 months), longer disease-free survival (6.3 months vs. 3.2 months), and a higher percentage of patients with baseline PSA reductions equal to or greater than 50\% (50\% vs 27\%).\textsuperscript{117} It is important to underline that the appropriate time to start docetaxel in hormone-resistant PCa patients has not yet been exactly determined, because they are a very heterogeneous group with different clinical characteristics.\textsuperscript{33,114,118}

Even when the positive effects of docetaxel in patients with hormone-refractory PCa have been proven, there...
is a population in which tumor disease progression continues; for this group of individuals newer compounds are used as second-line chemotherapy schemes, which include cabazitaxel. It is another chemotherapeutic drug that belongs to the taxane group, and that also acts by binding to microtubules.118 In a phase III study, the effectiveness and safety of cabazitaxel plus prednisone vs mitoxantrone plus prednisone was compared in 755 patients in whom disease progressed during or after treatment with docetaxel, the study reported that overall survival and disease-free survival were higher in the group treated with cabazitaxel (15.1 months vs 12.7 months and 2.8 months vs 1.4 months, respectively), as well as a 30% decrease in the risk for death.120

### PERSPECTIVES

Growth factors play an important role in tumor development, such as vascular endothelial growth factor (VEGF), that is responsible for the process of angiogenesis and neovascularization in normal, as well as in tumor tissues. There are pharmacologic compounds that act by directly inhibiting this growth factor or that block their natural receptors, such as bevacizumab and aflibercept.121 Bevacizumab is a human recombinant monoclonal antibody that is specifically directed to the peripheral VEGF receptor.116 In a recent phase III study the use of docetaxel/prednisone plus bevacizumab was compared with docetaxel/prednisone plus placebo, and it was observed that the antibodies directed to this growth factor reduced both prostate tumor cell growth as well as PSA levels, but did not increase overall survival in hormone-refractory PCa, and it was associated with more adverse events.116,122 In contrast, aflibercept is a drug that consists of a fusion protein that acts as a VEGF-A and VEGF-B receptor, however further studies are needed.123

There are other compounds such as sunitinib, sorafenib, and cediranib whose mechanism of action involves the inhibition of the tyrosine kinase receptor responsible for the activation of the VEGF receptors, the platelet-derived growth factor receptors (PDGF-R), and the stem cell factor receptor. However, they are still being studied and their clinical evaluation is pending.116

Therapies directed at avoiding or reducing the severity and progression of bone metastasis observed in metastatic PCa include compounds such as atrasentan, zibotentan, and denosumab, which bind endothelin to its receptor with an effect on mitogenic, anti-apoptotic, and bone-remodeling activity in metastatic PCa.124 Atrasentan is a compound that blocks the ET-1A endothelin receptor, inhibiting osteoblastic and angiogenic activity. However, in two phase III clinical studies it was not able to increase progression-free survival, which was the primary objective of the studies.125,126 The results of another phase III study (SWOG 0421) are pending.127 Zibotentan is another component of the endothelin receptor antagonists, but with greater specificity for ET-A, that showed effectiveness in bone metastatic hormone-refractory PCa by increasing overall survival in a phase II clinical study (24.5 months vs 17.3 months of placebo). Denosumab is a monoclonal antibody whose objective is to bond to the RANK ligand (RANKL), given that the activating receptor of the k B (RANK) nuclear factor promotes osteoclast activity and consequently increases the appearance of pathologic fractures in metastatic PCa patients.125 Its use was approved by the FDA in 2010 after showing greater effectiveness than zoledronic acid in increasing the time until the appearance of the first skeletal event such as spinal cord compression or pathologic fracture.127

Among the new cytotoxic agents being evaluated are satraplatin and the epothilones. Satraplatin is a chemotherapy agent that belongs to the family of platin derivatives that has been shown to delay disease progression and metastatic symptoms (35% lower risk for progression and 33% lower risk for symptomatic progression). However, it has not been able to increase overall survival.128 Ixabepilone, patupilone, MBS310705, KOS862, and ZK EPO are epothilones that act on microtubules by stabilizing them. Unfortunately their outstanding adverse events are neutropenia and sensory peripheral neuropathy.129 Clinical studies have shown that the combination of ixabepilone with estramustine achieved PSA baseline level reductions higher than 50% in 92% of the patients and that its application as a second-line chemotherapeutic agent for hormone-refractory PCa after docetaxel, resulting in an increase in mean survival of 9.8 months, when compared with mitoxantrone plus prednisone.118,130

The advances in hormonal therapy have been based on the concept that in the hormone-refractory PCa stage, the androgen receptor continues to be responsible for continuous tissue growth, and therefore drugs such as abiraterone acetate and MDV 3100 have been proposed to overcome this. On the one hand, abiraterone acetate is a P450 (CYP17A1) cytochrome inhibitor that inhibits the synthesis of both estrogens and androgens, since their precursor, cholesterol. However, it is associated with adverse events secondary to mineralocorticoid increase, such as high blood pressure and hypototassemia.132 The use of this drug combined with prednisone in patients that received previous chemotherapy with docetaxel, has been shown to increase overall survival.116 On the other hand, MDV 3100 is a stronger second generation antiandrogen (androgenic receptor antagonist) that inhibits the translocation of the androgen receptor to the nucleus and consequently blocks the signaling...
pathway.\textsuperscript{23,116} The phase III clinical study named AFFIRM showed that the use of this new drug reduced the risk for death and significantly increased overall survival (4.8 months longer than the placebo).\textsuperscript{131}

The use of vitamin D is another of the new therapeutic strategies for PCa, given that its antineoplastic effects have been proven in experimental studies with cell culture studies. It is known that part of the vitamin D metabolite, 25-OH Vit D, is normally hydroxylated in the prostate tissue— an ability that is lost in the LNPCa cell lines— leading to the theory that changes in the 1 alpha-hydroxylase function could make the prostate cells susceptible to the lack of control in the cell cycle.\textsuperscript{132} The effect of a calcitriol (DN-101) analog administered together with a chemotherapeutic agent (docetaxel) has been analyzed in preclinical trials, and the ASCENT-1 study showed that the combination had a greater impact on overall survival compared with docetaxel plus placebo, with no significant increase in adverse events. However, in the ASCENT-2 study, the administration of DN-101 was associated with a higher mortality rate, resulting in the discontinuation of both the study and the development of the compound.\textsuperscript{124}

\section*{CONCLUSIONS}

Initially, AB appeared to have cured PCa, but time has shown that is not the case. Therefore PCa is a frequent disease that continues to be the object of constant investigation in the search for the most appropriate therapy to provide patients with a better quality of life, free from significant side effects, and with a greater life expectancy. There is a wide gamut of available drugs for hormonal manipulation in hormone-sensitive PCa. However, it is important to consider patient characteristics from the medical and economic perspectives so that treatment can be individualized, thus satisfying the needs of each patient, and achieving the goal of reducing both the symptoms of the disease and the adverse effects caused by the treatment itself. In the face of PCa progression towards hormone resistance and the lack of effective drugs that promote greater survival in this group of patients, new therapies are underway that are the object of ongoing developmental and clinical evaluation directed at different levels of the disease pathogenesis, in an effort to gain a clearer understanding of its pathology and thus provide better therapeutic resources. For all of these reasons, PCa should be thought of as an evolving disease that needs newer curative therapies.

\section*{REFERENCES}


