TREATMENT REVIEW

Treatment of gynecomastia in patients with prostate cancer and androgen deprivation

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KEYWORDS
Prostate cancer; Hormone treatment; Gynecomastia; Mastodynia

Abstract

Context: Gynecomastia, defined as benign proliferation of glandular breast tissue has a prevalence of 32–72% in the male. In the urology setting, it is associated to patients with prostate cancer and hormone treatment with a prevalence of 15% in the case of complete hormone blockage and 75% in monotherapy. The different options of treatment in prostate cancer have changed in recent decades. Thus, we have focused on this subject to evaluate the different therapy options of hormone manipulation induced gynecomastia in prostate cancer patients.

Objective: To synthesize the available evidence on the different therapeutic options in prostate cancer patients who develop gynecomastia due to the use of nonsteroidal antiandrogens and to generate a diagnostic algorithm and treatment.

Acquisition of evidence: Using the PICO type structured search strategy (patient or problem, intervention, comparison, outcome or result) in the data bases of PubMed-Medline and Cochrane, identification was made of the relevant studies related to the treatment of gynecomastia in prostate cancer patients treated with nonsteroidal antiandrogens.

Synthesis of evidence: We have found 3 possible therapeutic options for the treatment of gynecomastia and mastodynia in patients with hormone deprivation therapy for prostate cancer. The 10 Gy radiotherapy would be an option for the treatment of gynecomastia, although not all the patients need prophylactic treatment since only 50% report moderate–severe discomfort. Another option is the use of drugs such as tamoxifen 20 mg/day that lead to a significant decrease in the mammary effects.

Conclusions: Gynecomastia and mastodynia, given their high incidence, make the physical examination a fundamental tool for all patients before initiating treatment with antiandrogens. The use of tamoxifen 20 mg/day is the best treatment and prevention option against gynecomastia and mastodynia, while in the case of long-course established gynecomastia, surgery is the gold standard.

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PALABRAS CLAVE
Cáncer de próstata; Tratamiento hormonal; Ginecomastia; Mastodinia

Manejo de la ginecomastia en pacientes con cáncer de próstata y deprivation androgénica

Resumen
Contexto: La ginecomastia, definida como una proliferación benigna de tejido glandular mamario, se presenta en el varón con una prevalencia entre el 32–72%. En el ámbito de la Urología se asocia a pacientes con cáncer de próstata y tratamiento hormonal, con una prevalencia del 15% en el caso de bloqueo hormonal completo y del 75% en monoterapia. Las diferentes opciones de tratamiento del cáncer de próstata han cambiado en las últimas décadas. Es por este motivo por lo que nos centramos en este tema para valorar las diferentes opciones terapéuticas de la ginecomastia causada por la manipulación hormonal en pacientes con cáncer de próstata.

Objetivo: Sintetizar la evidencia disponible sobre las diferentes opciones terapéuticas en pacientes con cáncer de próstata que desarrollan ginecomastia por el uso de antiandrógenos no esteroidéos, y generar un algoritmo de diagnóstico y tratamiento.

Adquisición de evidencia: Mediante el uso de estrategia de búsqueda estructurada tipo paciente problema, intervención, comparación, outcome o resultado (PICO) en la base de datos de PubMed-Medline y de la Cochrane se llevó a cabo la identificación de estudios relevantes relacionados con el manejo de la ginecomastia en pacientes con CaP tratados con antiandrógenos no esteroidéos.

Síntesis de evidencia: Nos encontramos con 3 posibles opciones terapéuticas para el manejo de la ginecomastia y la mastodinia en pacientes que realizan tratamientos de deprivation hormonal para el cáncer de próstata. La radioterapia 10 Gy sería una opción para el tratamiento de la ginecomastia, aunque no todos los pacientes necesitan un tratamiento profiláctico, ya que solo el 50% refieren molestias moderadas-severas. Otra opción es el empleo de fármacos como tamoxifeno 20 mg/d que ocasiona una disminución importante de los efectos mamaros.

Conclusiones: La ginecomastia y la mastodinia, dada su alta incidencia, hacen que la exploración física sea un arma fundamental para todos los pacientes antes de iniciar un tratamiento con antiandrógenos. El empleo de tamoxifeno 20 mg/d constituye la mejor opción para el tratamiento y la prevención de la ginecomastia y la mastodinia, mientras que en el caso de la ginecomastia establecida de larga evolución la cirugía es el patrón de oro.
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Introduction
Gynecomastia is defined as benign proliferation of breast glandular tissue. Gynecomastia can be unilateral or bilateral and may be accompanied with some discomfort described as tension and pain of varying intensity. It is caused by an increased proportion of estrogens with respect to circulating androgens, thus creating an imbalance in the proportion of androgens: estrogens in breast tissue. It is necessary to differentiate it from pseudogynecomastia, which consists of an enlargement of the fatty deposit in the breast area without an enlargement of accompanying glandular tissue.

Histologically, in the first stages of gynecomastia there is a proliferation of the glandular ducts accompanied by epithelial hyperplasia and an increased stroma with greater vascularization and periductal edema. When gynecomastia becomes chronic and perpetuates itself for more than a year, there is a decrease in ductal proliferation and stromal hyalinization and fibrosis occur, this being an irreversible process. In males, it may be due to physiological causes, or in some cases by pathological causes such as cirrhosis, malnutrition, testicular tumors, hyperthyroidism, dialysis and drugs from the calcium channel blockers family, H2 receptor blockers, aldosterone antagonists and, in our field, drugs for hormonal treatment of prostate cancer (PCa), which create an imbalance between estrogens and androgens. The prevalence of drug-induced gynecomastia is around 10–20%.

Gynecomastia, in turn, has a prevalence which ranges between 32 and 72% with a bimodal peak of incidence. The first peak occurs at puberty, with a prevalence varying between 4 and 69%, and the second peak occurs between the fifth and eighth decades of life, with a prevalence of around 24–65% . These wide differences in prevalence are due to differences among observers and to the difference in the age distribution of the examined teenagers. This first peak is physiologic gynecomastia, since estradiol levels increase to adult levels earlier than testosterone, resulting in an imbalance which comes to an end when reaching adult testosterone levels. In the case of the second peak, that difference in prevalence is also due to the existing differences in age distribution and among observers. In this second group, we must take into account that there was a group, which accounted for 25%, where we did not find the cause for gynecomastia, and drugs, which also accounted for 10–25%.

In the Urology field, gynecomastia is mainly associated with patients receiving hormone therapy for PCa. The prevalence of gynecomastia is 15% in those patients with complete hormonal blocking and increases to 75% when antiandrogens are used in monotherapy, and it may be
a reason for stopping DA in 16.4% of cases.\textsuperscript{1} The different treatment options for PCAs have changed over the last decades. In addition to the use of hormone therapy in advanced stages, it is increasingly being used as adjuvant treatment in patients with locally advanced PCAs, as well as therapy for patients with biochemical relapse after curative treatment. We focused on this issue for this reason, in order to assess the different therapeutic options for gynecomastia caused by hormone manipulation in patients with PCAs.

**Objective**

To synthesize the available evidence on the different therapeutic options in those patients with PCAs who develop gynecomastia, caused by the use of non-steroidal antiandrogen drugs, and to provide a diagnosis and treatment algorithm.

**Evidence acquisition**

By using a structured search strategy in the format patient problem, intervention, comparison, outcome (PICO) in the PubMed-Medline and Cochrane databases, we carried out the identification of relevant studies related to the management of gynecomastia in patients with PCAs treated with non-steroidal antiandrogen drugs. The cross-reference list of all the relevant articles was also reviewed. The search was performed with no limitation in terms of date, language, or type of study, and all the studies up to 2012 were included. A total of 126 articles were found.

The assessment for inclusion of the studies identified in our search was based on criteria such as the type of study, including any kind of study where the subject matter was analyzed, with the exception of case series and conference proceedings. The type of participants was another criterion which included male adult patients with a diagnosis of advanced PCAs on androgen deprivation therapy. The type of intervention refers to non-invasive measures, such as radiotherapy or medical treatment with tamoxifen or anastrozole, and to invasive measures such as surgery. The type of main outcomes were gynecomastia and mastodynia control in patients treated with non-steroidal antiandrogen drugs. A reading of titles and abstracts was performed to check whether they met the selected criteria. A critical reading of the selected articles was performed to identify possible biases and methodological deficiencies affecting their validity, and, thereby, to extract data. Those studies in early stages of clinical trials, conference proceedings, and clinical case series were excluded. Those studies that were not focused on our type of participants, type of intervention, and comparison were excluded. 6 articles in total were chosen for our discussion.

**Evidence synthesis**

Treatments for prostate cancer which cause gynecomastia

The main premise for the hormonal treatment of PCa is that testosterone stimulates cancerous tissue. Thus, the goal of PCa treatment with hormonal manipulation is to eliminate circulating androgens, and/or to eliminate its effects on cancerous tissue by blocking androgen receptors. These changes in the hormonal milieu alter the relationship between estrogens and androgens, increasing the likelihood of gynecomastia.

The normal physiological functioning of the hypothalamic-pituitary-gonadal axis (Fig. 1) is the production of gonadotrophin-releasing hormones by the hypothalamus, which stimulates LH, FSH and ACTH release from the pituitary gland. These hormones stimulate androgen secretion by the testicles and the adrenal glands. Testosterone, through a negative feedback mechanism, inhibits the release of gonadotrophin-releasing hormones. Moreover, testosterone undergoes an enzymatic effect by the 5α-dihydrotestosterone to DHT, and some peripheral flavoring to estradiol, at 1:100 ratio.

The incidence of gynecomastia will vary depending on the treatment used. In the case of bilateral orchiectomy (Fig. 2), there is a significant decrease of testosterone. However, in the adrenal gland, there is an increase in androstenedione production, which is converted to estrone by a flavoring mechanism. Estrone is subsequently converted to estradiol by peripheral conversion. Estradiol stimulates breast tissue causing mastodynia and gynecomastia.

When we used antiandrogens (Fig. 3), both steroidal and non-steroidal ones, they blocked the androgen receptors existing in breast tissue, so there was no inhibitory effect of testosterone on breast tissue. Furthermore, non-steroidal or pure antiandrogens cause inhibition of pituitary androgen receptors, so there is no negative feedback of testosterone and, thus, an increase in LH and FSH will occur, so there will be an increase of testosterone and an increase of that peripheral conversion of testosterone to estradiol which will affect the breast causing gynecomastia and mastodynia\textsuperscript{4,7} (Table 1).

The frequency of occurrence of gynecomastia with the use of antiandrogens with gonadotrophin-releasing hormone agonists is about 15%, but the frequency of gynecomastia with antiandrogens in monotherapy is rather similar; thus, we found gynecomastia rates of around 43–76% with flutamide, 79% with nilutamide, and between 47 and 85% with bicalutamide.\textsuperscript{4,8}

**Treatment of gynecomastia**

3 possible therapeutic choices are currently available for the management of gynecomastia and mastodynia in patients who undergo hormonal deprivation therapy for PCAs. The incidence of gynecomastia, though variable, is rather high in those patients undergoing non-steroidal antiandrogen therapy. In the fourth analysis performed by the Early Prostate Cancer program (EPC), gynecomastia and mastodynia were identified in 68.8 and 73.7% of the patients treated with bicalutamide 150 mg.\textsuperscript{9} Nevertheless, in over 90% of the cases, such events were mild to moderate in intensity.\textsuperscript{10} On the other hand, when gynecomastia has been present for at least a year, it causes irreversible and permanent alterations in the breast.\textsuperscript{8} That is why we must focus on our possible therapeutic choices for the management of gynecomastia
Treatment of gynecomastia in patients with prostate cancer

in a preventive way, before medical treatment or during treatment.

Suspension of treatment

We might consider the suspension of the treatment prescribed as a first choice; this would eliminate gynecomastia in 70–90% of cases, reducing the chances of regression as the duration of hormone treatment is prolonged. However, the suppression of androgen receptor blockade may lead to regrowth of PCa tumor cells. Besides, gynecomastia is not dose-dependent, and lower doses of antiandrogens are not indicated for the treatment of PCa, so it is advisable to continue treatment and to focus on other therapeutic choices.

Breast radiotherapy

Radiotherapy (RT) is another major option for the treatment of gynecomastia; even when prophylactically used, it significantly decreases the incidence of this disorder, although it does not seem to alleviate mastodynia. It has been noted that a single 10 Gy dose of electron beam RT significantly reduces the incidence of gynecomastia associated with the use of antiandrogens, since those patients preventively treated with RT showed an incidence of gynecomastia of 52%, whereas its incidence in those who underwent simulated RT, that is, placebo, along with antiandrogens was 85%. Similar outcomes were reported in 3 clinical trials, where prophylactic RT was given at doses between 10 Gy and 15 Gy. Gynecomastia occurred in 72% of those patients treated with antiandrogens when compared with the group

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Table 1  Characteristics of the selected articles.

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of patients</th>
<th>Group</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ozen et al.</td>
<td>125</td>
<td>R</td>
<td>RT vs no RT</td>
<td>RT &lt; 0.001</td>
</tr>
<tr>
<td>Fradet et al.</td>
<td>282</td>
<td>R</td>
<td>Tamoxifen different doses</td>
<td>20 mg/day better</td>
</tr>
<tr>
<td>Saltzstein et al.</td>
<td>107</td>
<td>R</td>
<td>Tamoxifen vs anastrozole</td>
<td>Tamoxifen better</td>
</tr>
<tr>
<td>Perdona et al.</td>
<td>51</td>
<td>R</td>
<td>Tamoxifen vs RT</td>
<td>Tamoxifen &gt; RT</td>
</tr>
<tr>
<td>Di Lorenzo</td>
<td>102</td>
<td>R</td>
<td>Tamoxifen vs RT</td>
<td>Tamoxifen &gt; RT</td>
</tr>
<tr>
<td>Tyrrel</td>
<td>106</td>
<td>R</td>
<td>RT vs placebo</td>
<td>RT &lt; 0.001</td>
</tr>
</tbody>
</table>

R: randomized; RT: breast radiotherapy.
treated with RT and antiandrogens, where gynecomastia occurred in 33% of them. Established gynecomastia may be treated with higher radiation doses (20 Gy in 5 fractions), with an improvement in pain, but being less effective when reducing breast volume. It has been reported that prophylactic RT avoids the development of gynecomastia, but not in all cases. For this reason, the Ozen group, from Ankara University, wondered if prophylactic RT would be necessary in all patients with PCa. In their research, they observed that the real incidence of gynecomastia is controversial, ranging between 40 and 80% according to current literature. On the other hand, there is a discrepancy between gynecomastia perceived by the patient and by the doctor, since diagnosis depends on the operator. Similar results may be observed in the studies performed by Tyrrel and Widmark, which showed a lower rate of gynecomastia among those patients who underwent RT when compared with those who were not treated that way. Besides, the percentage of moderate to severe mastodynia was very low. That was why Ozen concluded that not all patients require prophylactic therapy, since only 52% of them were moderately or severely affected and concerned about gynecomastia.

Medical treatment

Another option for the management of gynecomastia in patients treated with antiandrogens in monotherapy is to antagonize estrogen receptors. In order to do this, several drugs are available, such as tamoxifen and anastrozole. In the study carried out by Fradet et al., they observed that tamoxifen 20 mg/day, administered with bicalutamide 150 mg, reduced the incidence of breast events in 6 and 12 months. In this research, tamoxifen treatment was suspended after 12 months. However, 90% of patients experienced breast events a year later, so it is advisable to continue treatment with estrogen receptors antagonists while taking antiandrogens.

We wondered which tamoxifen dosage was appropriate for the management of gynecomastia; in the multicenter study by Bedognetti et al., it was observed that the application of tamoxifen 20 mg/day is more effective than its weekly application. Besides, it has been reported that tamoxifen does not affect or modify neither prostate cancer nor the tumoral activity caused by antiandrogens, although the available evidence suggests good effectiveness of tamoxifen for the prevention and treatment of gynecomastia induced by antiandrogens. Further randomized clinical trials are needed on the long-term impact of tamoxifen in terms of adverse effects, disease progression, and survival, since it still remains uncertain. Saltzstein et al. compared in a randomized clinical trial breast events in patients undergoing monotherapy with bicalutamide, a second group receiving this same treatment in combination with tamoxifen, and a third group, where that
combination was made with an aromatase inhibitor such as anastrozole. In the first group, gynecomastia occurred in 73% of patients and mastodynia in 39%; in the second one gynecomastia occurred in 10% of them, and mastodynia in 6%, and in the last group the percentages were 51 and 27%, respectively. Data collected by Perdona et al. showed a lower rate of gynecomastia and mastodynia in the group treated with tamoxifen than in the groups treated with radiotherapy or in monotherapy, 8 and 6% for the tamoxifen group, 34 and 30% for the radiotherapy group, 69 and 57% for the group treated only with antiandrogens.

The following question arises here: which would be the best choice for the management of gynecomastia in men with PCa treated with antiandrogens? The review carried out in this article showed that tamoxifen, radiotherapy and anastrozole prevent and reduce mastodynia and gynecomastia. However, from the reviewed studies, we can deduce that tamoxifen is more effective than other choices.

**Surgery**

In those patients with long-standing gynecomastia, where breast tissue fibrosis is possible, removal of breast tissue with surgery remains the gold standard.

**Proposed systematic study of gynecomastia**

Thus, before starting any hormone treatment in a patient with a diagnosis of PCa, we must ask him questions about increases in size or pain symptoms or breast turgidity. We will perform a breast examination, using the Marshall–Tanner stages to determine the degree of hypertrophy and to measure breast size in centimeters, being able to detect it when it is larger than 0.5 cm. An evaluation with mammography and breast ultrasound would allow us to confirm the diagnosis in case of doubts. Despite the fact that gynecomastia is common, there is no consensus on how to define or classify the severity of this condition.

In our current routine clinical practice, we use the following algorithm. All patients with PCa who are going to undergo hormone therapy are examined in medical consultation to discern whether they suffer from gynecomastia or not. If so, we should ask questions about other possible causes for gynecomastia, such as other drug use, and make a differential diagnosis with other diseases that cause it. If the patient does not suffer from gynecomastia, it will be necessary to explore and ask him about it in regular examinations. If they develop gynecomastia with mild or moderate mastodynia, we will manage it with NSAIDs; in those cases of gynecomastia with severe symptoms, we will add tamoxifen 20 mg/day treatment.

**Figure 3**  Physiology of the hypothalamic–pituitary–gonadal axis after administration of nonsteroidal antiandrogens.
Conclusion

Gynecomastia and mastodynia, though benign processes, have high incidence in the population between 50 and 80 years age, so it is very important to explore all patients before starting antiandrogen treatment, since it may occur before therapy. In spite of its high incidence, most patients show events of mild-to-moderate intensity, so mastodynia can be managed with painkillers. The last reviews reported superiority of tamoxifen 20 mg/day versus RT in the prevention and treatment of gynecomastia and mastodynia. In the case of long-standing established gynecomastia surgery is the gold standard.

Conflict of interest

The authors declare that they have no conflict of interest.

References