

Chapter 06 / Capítulo 06

Advanced Prostate Adenocarcinoma and Androgen Deprivation Therapy. Clinical Outcomes, Risk Stratification, and Therapeutic Results

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Clinical discussion and implications

Prostate cancer is a hormone-dependent neoplasm with significant heterogeneity. Clinical behavior, response to treatment, and survival vary depending on the patient. More than 95 % of prostate cancers are adenocarcinomas. The risk of prostate adenocarcinoma increases with age, especially after 50 years, but more than 80 % of patients over 65 years of age are diagnosed with prostate adenocarcinoma. In a study of progression according to the type of treatment applied, published in the Spanish Urological Journal, the average age was 74,33 years. A case-control study on prostate cancer risk factors conducted by the National Institute of Oncology and Radiobiology in 2015 revealed that patients aged 65--84 years accounted for 89 % of the cases related to population aging. The results of this research coincide, with the over 70 years of age group having a 61 % high risk and 58 % very high risk.⁽⁶⁹⁾

A lack of adherence to treatment in the context of oncological diseases is considered a serious health problem. It is a very complex process that requires education and support for the patient to achieve active and responsible participation in treatment. Nonadherence to treatment in 2019 was more representative, with seven patients due to instability in the supply of pharmacological treatment to the center, followed by 2020, where the epidemiological situation had an impact, with a decrease in attendance at follow-up appointments and medication collection.

Currently, most prostate cancer cases are diagnosed in the early stages, whereas only 5-10 % are diagnosed at advanced stages. The biological and clinical progression rates of T1 and T2 prostate adenocarcinomas are 11,36 % and 9,09 %, respectively.⁽⁷⁰⁾

During the study, depending on the risk classification, progression to advanced stages occurred in 13,7 % and 12,3 % of very low-risk and low-risk patients, respectively. Moreover, 34 patients at intermediate risk progressed.

Bone metastases were the most frequent sign of disease progression in the present study, accounting for 49,3 %, with the highest incidence occurring at 3 years. A total of 10 patients developed lymphadenopathy, with the highest incidence occurring one year after treatment. Renal failure occurred in a total of 2 patients, accounting for 10 % of the total.

Hormone-sensitive advanced prostate cancer accounts for approximately 3 % of prostate cancer cases in the US, approximately 6 % in Europe, nearly 60 % in the Asia-Pacific region, and approximately 40 % in Latin America, and its incidence is increasing.

Although patients generally respond initially to androgen deprivation therapy, most progress to hormone resistance within 12-15 months. After hormone therapy, a reduction in PSA to undetectable concentrations provides information regarding the duration of disease progression-free status; however, a decrease in PSA to less than 80 % may not be very predictive. Because PSA expression itself is under hormonal control, androgen deprivation therapy can decrease the serum PSA concentration regardless of the tumor response. Consequently, the serum concentration alone cannot be relied upon to monitor a patient's response to hormone therapy; clinical criteria must also be considered.⁽⁷¹⁾

The serum behavior of testosterone and prostate-specific antigen in patients with prostate carcinoma between 2013 and 2015 in the province of Holguín revealed that the ratio of blood

testosterone and PSA values reflected those 101 patients with serum testosterone levels below 38 nmol/L and 3 had elevated levels. Among the patients studied, 89 had significantly elevated PSA blood levels, and 15 had values between 10 and 20 ng/ml, with a coefficient of variation of 2,9 for the serum testosterone level and 2,3 for the PSA level. The results of this research revealed that, after three years, testosterone increased, representing 86,4 % of the 19 patients, constituting a fundamental parameter for determining the moment of hormonal escape. The increase in the PSA level after one year constituted 52,6 % of the variation and was a sign of disease progression.^(72,73)

Zoledronic acid is a third-generation bisphosphonate that is most commonly used for the treatment of bone metastases. It is approved for the prevention of bone complications in patients with advanced neoplasms affecting the bone.

Figure 2 shows that of the 36 patients with metastatic lesions who received zoledronic acid, 24 completed the treatment, whereas the results were inconclusive for 12 patients because of signs of renal failure with elevated creatinine levels secondary to nephrotoxicity. Follow-up scintigraphy revealed improvement in previous metastatic lesions in 20 patients but was unfavorable for 4 of them, where the lesions persisted.

Mundy et al. conducted a review of preclinical studies with bisphosphonates and reported a reduction in bone metastases. Green JR also conducted a preclinical review of the antitumor effects of bisphosphonates.⁽¹⁸⁾ Based on these effects, a variety of potential mechanisms have been proposed: indirect effects on tumor cell growth in bone through the inhibition of bone resorption and osteoclastogenesis; induction of tumor cell apoptosis; inhibition of tumor cell adhesion to the extracellular matrix; reduction in metastatic potential; and inhibition of angiogenesis. Multiple in vitro studies have been conducted to demonstrate the antitumor activity of zoledronic acid. Corey et al. studied the effect of zoledronic acid on bone metastases in rats and reported that zoledronic acid did not affect prostate tumor growth but did inhibit the growth of osteoblastic and osteolytic metastases, exhibiting antitumor activity both in vitro and in vivo.⁽⁷⁴⁾

CALGB-90202 was a randomized controlled trial comparing zoledronic acid (4 mg IV every 4 weeks) and placebo in 645 men with androgen deprivation-sensitive prostate cancer who had bone metastases. Patients with disease progression and resistance to hormone therapy received zoledronic acid without treatment masking.⁽⁴⁸⁾

There was no difference between the two study groups in the primary endpoint of skeletal complications (defined as clinical fractures, spinal cord compression, episodes requiring palliative radiation or bone surgery, and death from prostate cancer) after a maximum follow-up of 7 years.^(75, 76)

Androgen deprivation is associated with side effects such as obesity, erectile dysfunction, gynecomastia, insulin resistance, lipid metabolism disorders, loss of bone density, fatigue, and cognitive impairment, which impact patients' quality of life; it sometimes causes osteoporosis and bone fractures.

In a population sample of 50 613 Medicare patients aged 66 years or older who were followed for a median of 5,1 years, men treated with a gonadotropin-releasing hormone (GnRH) agonist or with orchiectomy had a bone fracture rate of 19,4 %, whereas this rate was 12,6 % for men

who did not receive hormone deprivation therapy. The effect was similar in men with or without metastatic bone disease. In randomized placebo-controlled trials, treatment of osteoporosis with bisphosphonates was found to reduce the risk of bone fractures in men.^(77, 78)

This evaluation revealed that at the start of anti-androgen treatment, there was a drastic reduction in patients' erectile function and sexual desire, leading to erectile dysfunction in 48 % of patients. Gynecomastia and mastodynia accounted for 16 % and 14 %, respectively, of cases, followed by hot flashes or hot flushes, as they are often described, accounting for 10 %, and to a lesser extent, bone pain and hepatotoxicity.