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GNRH ANALOGUES AND ITS ROLE IN CRPC

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ABSTRACT: *Prostate cancer is the most common cancer for men in Europe and it is in the first place for incidence in Italy. In almost all cases occur in men over 70 years old with a 5 years overall survival of approximately 88%. Prostate cancer is a multifactorial disease and it is the result of a complex interaction of genetic and environmental factors. Today newer forms of androgen-deprivation therapies remain the first line treatment for this disease. Currently androgen deprivation can be achieved through several mechanisms: surgically (bilateral orchiectomy) or medically (GnRH agonists and antagonists, anti-androgens or estrogens). Advanced age and the presence of biologically active androgens, in the circulating blood and prostate tissue, represent the most important causal factors related to the tumour. The medical treatment represents the standard of care and GnRH agonists and antagonists are the first choice of treatment in both phases of the natural history of tumor (locally advanced and metastatic setting) with continuously or intermittent modality. Osteoporosis, loss of erectile function, gynecomastia, and metabolic syndrome are some of typical side effects of androgen deprivation therapy. Unfortunately, due to prostate cancer heterogeneity, in most cases, despite an excellent initial response, the tumour will progress through treatment to a hormone refractory (HRPC), androgen independent (AIPC), or castration resistant prostate cancer (CRPC) stage. The use of GnRH analogues may contribute to the control of tumour growth and maintenance of the castrate state is an essential component in the treatment of patients who progress while on hormonal therapy. Current national and international guidelines recommend continuing with androgen deprivation, LHRH analogues, in association with subsequent treatments (chemotherapy and next generation hormonal-therapies).*

KEY WORDS: *CRPC, GNRH analogues, Prostate cancer, Hormone therapy.*

Prostate cancer is the most common cancer for men in Europe. The age-standardized incidence rate is 86.7 cases/100,000 individuals, while the death rate is 22.2 deaths/100,000[1]. The aggressiveness of this disease varies considerably among the same histology. In Italy, prostate cancer is in the first place for incidence and in the third in regard to mortality[2]. In almost all cases, it occurs in men over 70 years of age. Currently, the overall survival of patients with prostate cancer is approximately 88% at 5 years after diagnosis, but it is in constant and significant improvement[2].

Prostate cancer is a multifactorial disease and is the result of a complex interaction of genetic (family, history, race) and environmental (dietary factors, environmental carcinogens) factors.

Advanced age and the presence of biologically active androgens in the circulating blood and

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prostate tissue, represent the most important causal factors[3,4]. The concept of androgen deprivation for the treatment of advanced prostate cancer was developed more than 50 years ago[5] and today newer forms of androgen-deprivation therapies remain the first line treatment for this disease. The principle behind reducing the levels of circulating androgens for therapeutic purposes is based on the central role that this hormones have on the development, differentiation and maturation of male reproductive organs, including the prostate. Androgens are synthesized primarily in the testis, under the regulation of luteinizing hormone, which is itself regulated by the levels of gonadotropin releasing hormone (GnRH), in the adrenal glands and secondarily in peripheral tissues including the prostate. Testosterone (T) is the principal androgen and circulates mostly (98%) bound to sex hormone-binding globulin and albumin. Intracellularly, T is enzymatically converted to the more potent metabolite dihydrotestosterone (DHT); both steroids bind to the androgen receptor (AR), a ligand-regulated transcription factor in the nuclear hormone receptor super family. Liganded-AR binds to the androgen response elements present in the regulatory regions of a variety of genes involved in the growth, survival, and differentiation of prostate cells[6-8].

Androgen deprivation can currently be achieved through several mechanisms: surgically (bilateral orchiectomy) or medically (GnRH agonists and antagonists, anti-androgens or estrogens). The medical treatment represents the standard of care and GnRH agonists and antagonists are the first choice of treatment. There are several formulations of GnRH, administered every month or every three or six months, allowing greater compliance and improving the quality of life of patients. These formulations are able to get a proper medical castration (testosterone levels <20 ng/dl) in 93.7% of cases for the monthly and in 90.6% for the three-month administration.

Androgen deprivation, although well tolerated, is associated with some side effects, particularly in the long term treatment, such as: osteoporosis, loss of erectile function, gynecomastia, cognitive dysfunction and loss of muscle mass. In addition, cardiovascular problems and metabolic syndrome have also been described[9], although Nguyen et al[10] did not find significant differences in the rate of death from any cardiovascular causes among patients treated with androgen deprivation. To minimize the development of side effects, different trials have evaluated the clinical role of intermittent hormone therapy compared to the continuous administration, also in the hypothesis that intermittent therapy could delay the androgen independence[11]. Two large phase III trials have reported results comparing these two forms of ADT administration. The National Cancer Institute of Canada (NCIC) PR-7 trial studied men with an increasing prostate-specific antigen (PSA) level and no evidence of metastatic disease after definitive or salvage radiation therapy and radical prostatectomy. The Southwest Oncology Group 9346 trial studied men with newly diagnosed hormone-sensitive metastatic disease. The primary end point in both trials was overall survival with a not inferiority design. The NCIC trial showed that the overall survival in men treated with intermittent ADT was not inferior to that of men treated with continuous ADT, but the SWOG trial was inconclusive regarding non inferiority. Quality of life was better in the intermittent arms of both trials. If using ADT in the setting of biochemical relapse, intermittent ADT should be strongly considered over continuous ADT, except perhaps in patients with Gleason score of 8 or higher. In men with metastatic disease, continuous ADT remains the standard of care, because the SWOG trial did not establish not inferiority of intermittent ADT with respect to survival[12,13].

Despite an excellent initial response, in most cases, the tumour will progress through treatment to a hormone refractory (HRPC), androgen independent (AIPC), or castration resistant prostate cancer (CRPC) stage and once this occurs the median survival is between 18 and 24 months. The precise definition of CRPC remains controversial. A practical recommendations to define CRPC are: castrate serum testosterone < 50 ng/dL or 1.7 nmol/L plus either biochemical progression (three consecutive rises of PSA, 1 week apart, resulting in two 50% increases over the nadir, with PSA > 2 ng/mL) or radiological progression (the appearance of two or more bone lesions on bone scan or enlargement of a soft tissue lesion using RECIST (Response Evaluation Criteria in solid tumours). Our knowledge of the mechanisms involved in the development of CRPC remains incomplete, but is starting to become clearer. An alteration in normal androgen signaling is thought to be central to the pathogenesis of CRPC. It is mediated through two main, overlapping, mechanisms, which are[14-21]:

Androgen-receptor (AR)-independent associated with the deregulation of apoptosis through the deregulation of oncogenes such as bcl-2 and p53.

AR-dependent such as: increased expression of AR with AR gene amplification (30% of cases), selection of AR mutants that can result in activation by non- androgenic ligands or mutations in other regions such as the amino terminus or the DNA binding domain that confer oncogenic properties to the AR, alterations in the balance between AR and its transcriptional co-regulators such as

TIF2, SRC1, and TIP60 that have been shown to be overexpressed or accumulated in the nucleus of recurrent prostate cancer specimens, and increased expression of enzymes involved in steroidogenesis such as FASN, CYP17A1, HSD3B1, CYP19A1.

The CRPC is an extremely heterogeneous disease and despite the different pathophysiological mechanisms involved, the current national and international guidelines recommend continuing with androgen deprivation, LHRH analogues, in association with subsequent treatments. There are little information available on the impact of continued androgen suppression on disease outcome in CRPC undergoing chemotherapy or other treatments. Manni et al[22] was the first to evaluate this issue, showing worse outcome in patients with advanced disease and treated with androgen priming and chemotherapy. Over the past few years, one of the prerequisites of the majority clinical trials, particularly those proposed by the Southwest Oncology Group (SWOG) has been discontinuation of hormonal therapy before initiation of chemotherapy. It is unclear whether termination of medical castration therapy is detrimental in terms of accelerated tumour growth. It has been postulated that discontinuation of androgen suppression in not orchiectomized patients may influence the outcome of these trials in terms of response and survival. Although not well studied, the issue revolves on the potential ability of a renewed release of testosterone and possible stimulation of remaining androgen-sensitive elements. Maha Hussain et al failed to show obvious advantages in response to chemotherapy or survival for patients with continued gonadal suppression[24]. These data have been challenged by another trial that showed only a marginal survival benefit for patients remaining on LHRH analogues during second- and third-line therapies[24]. Recent advances on the pathophysiology of prostate cancer development suggest that the role of androgens remains central in the different phases of prostate cancer, including CRPC. The assumption is that the constitutive cell population is extremely heterogeneous and a part of it, variable from tumour to tumour and in different metastatic sites, remains sensitive to androgenic stimulation, even in the presence of activation of growth pathways alternative to those of AR. The use of GnRH analogues may contribute to the control of tumour growth and maintenance of the castrate state is an essential component in the treatment of patients who progress while on hormonal therapy[25,26]. In effect, before the advent of new drugs, hormonal manipulation including addition of anti-androgens, anti-androgen withdrawal and oestrogens such as diethylstilboestrol (DES), however, allowed a good clinical control of the disease, although without advantages in overall survival[27]. In addition the suspension of hormone is likely to lead to a potential reactivation or up regulation of androgen receptors and, paradoxically, a rebound resulting in tumour growth. Recent evidences suggest that LHRH and its receptor (LHRH-R) are not limited to the hypothalamic-pituitary axis. In the periphery, the LHRH system regulates gonadal functions and appears to serve as a growth factor of benign conditions[28,29] and various cancers including breast, lung, ovary, endometrial, kidney, bladder, colon, pancreas and prostate[30,31]. A specific, medium to high-affinity binding site for an LHRH agonist was found in 86% of prostate cancers[30,31]. In addition, expression of LHRH receptor by prostate cancer cells is preserved even after a prolonged exposure to LHRH agonist; LHRH receptors also appear in lymph node metastases[31]. These findings imply that the LHRH receptor is a suitable object for the design of an approach based on targeted chemotherapy. Accordingly, various cytotoxic conjugates of LHRH have been produced of which AEZS-108 (previously known as AN-152) has been chosen for clinical development[29-31]. This compound consists of an agonistic analogue of LHRH, [D-Lys6]-LHRH, linked to the cytotoxic anthracycline, doxorubicin[32]. All registration trials of new drugs currently in use included the concomitant treatment with LHRH analogues[33-39]. In conclusion, the current evidence suggests that the metastatic CRPC maintains a testosterone-dependence in any stage. All the new drugs approved for CRPC are registered in association with LHRH analogues whose real clinical benefits is not clear. However, in the absence of prospective data, the modest potential benefits of a continuing castration outweigh the minimal risk of treatment, so current national and international guidelines recommend continuing with androgen deprivation, LHRH analogues, in association with subsequent treatments. This principle applies to first-line chemotherapy (docetaxel) for the second-line (cabazitaxel), and for the next generation hormonal-therapies (abiraterone and enzalutamide). This strategy is sanctioned by major national and international guidelines (AIOM, EAU, ESMO)[4,40].

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