INTRODUCTION

Prostate cancer (PC) has been recognized as a clinical entity long time ago, when it was first described by the ancient Egyptians, while surgical procedures to remove the prostate were developed >100 years ago.[1]

PC is the most reported male cancer as well as the second leading cause of cancer-related deaths in Western men, excluding non-melanoma skin diseases. [2]

Old age, black races, and a family history of the disease are the risk factors most commonly associated with PC. The average age at the time of diagnosis is 67 years and about two-thirds of cases are diagnosed in men aged 65 years and over-diagnosis before age 40 years is rare. Environmental risk factors such as eating habits, early sexual initiation, and sexually transmitted infections, both viral (herpes simplex virus 2, human papillomaviruses 18 and 16, and human cytomegalovirus) and bacterial (Neisseria gonorrhoea, Treponema pallidum, and Chlamydia trachomatis), are also associated with the disease. [3]

In terms of geographic variation, developed countries account for about 72% of all diagnosed PC cases and 53% of all deaths related to the condition. PC incidence is high in Australia and New Zealand, whereas South-Central Asia has the lowest incidence rate. Variation in PC incidence is partly

attributed to differences in access to diagnostic and treatment procedures. [4]

This disease is age-related, therefore, as life expectancy increases, so will its incidence, creating a significant health problem. [5]

Like most other solid malignancies, PC can metastasize to distant organs such as the liver, lungs and brain, but it has an unusually high propensity for metastasizing to the bone [6]

Depending on the disease state, the current treatments for PC include radiotherapy (RT), surgery, and androgen deprivation therapy (ADT). [7]

The successful management of PC requires early detection of clinically significant disease, appropriate risk assessment, and optimum treatment.[8]

The ability of radical prostatectomy or RT to significantly reduce PC mortality must await the results of ongoing clinical trials, yet on the basis of current rates of biochemical, i.e., serum prostate-specific antigen (PSA),failure it appears that they will not be sufficient as single modalities. In patients treated with radical prostatectomy, increased serum PSA levels indicative of local tumor recurrence and/or metastases occurs within five years in 20% to 57% of the men.[9]

However, advanced castrate resistant PC (CRPC) or metastatic disease continues to challenge medical management, which can offer only palliative care in most of these cases. Therefore, effective treatment and management of advanced PC is still an important preoccupation in clinical practice. [10]

Aim of the Work

The aim of this study is to compare different modalities in management of advanced prostate cancer.

Chapter One

PATHOGENESIS OF PROSTATE CANCER

Many pathologies affect prostate gland, such as PC, which is the most common non-cutaneous malignant cancer in Western male populations. A complex interaction between genetic and environmental factors (i.e. infectious agents, dietary carcinogens) and hormonal imbalances has been reported to have a fundamental role in PC pathophysiology by causing chronic inflammation. Thus, chronic inflammation drives prostate carcinogenesis and neoplastic progression.[12]

Host genetic factors may have an important role in the pathophysiology of most human cancers like PC. Evidence on its clinical features proposes PC as a latent and clinical cancer characterized by multifocal histologic patterns. Primary tumors often contain multiple, independent histologic foci, which are often genetically distinct. However, PC seems to arise from selective and individual clones during its progression.[13]

Chronic inflammation contributes to many forms of cancer. Cancers often arise as the end stage of inflammation. Approximately 20% of adult cancers affecting the liver, esophagus, stomach, large intestine and prostate are due to chronic inflammatory conditions caused by infectious agents, chronic non-infectious inflammatory diseases and/or other environmental factors. Thus, chronic inflammation is now

regarded as an 'enabling feature' of human cancer. It seems to influence the cancer pathogenesis by:

(i) Causing cell and DNA damage.

(ii) Triggering restorative cell proliferation to replace damaged cells.

(iii) Creating a tissue-rich microenvironment in cytokines, chemokines and growth factors that can enhance cell replication, angiogenesis and tissue repair. In addition, there is a complex interplay among host immune cells during neoplastic development, having both the ability to promote cancer and to limit or eliminate it. Inflammatory/immune cells and soluble factors have indeed been observed in all tissues and organs with Furthermore, the signs of 'smoldering' inflammation (i.e. tissue remodeling, angiogenesis and other wound healing-like features) are also commonly used by pathologists as morphologic signs of invasive cancer.[14]

Other evidence demonstrates that these stromal processes have a fundamental role in cancer development and progression, and, at least in some cases, may predict the clinical behavior of a cancer better than the characteristics of the neoplastic cells themselves. In addition, oncogenes seem to be involved in targeting proinflammatory pathways directly or indirectly. In both circumstances, the resulting host response is inflammation, which promotes tumor invasion and growth.[15]

Furthermore, several pathways linking inflammation and cancer have been identified:

- An intrinsic one, driven by genetic events that cause neoplasia.
- Extrinsic one, driven by inflammatory conditions that predispose to cancer.

The intersection between intrinsic and extrinsic pathways includes transcription factors, particularly nuclear factor-κB (NF-κB). NF-κB is a cytoplasmatic sensor constituted by a protein complex and inhibited commonly by binding to IκB proteins. It modulates the inflammatory response by mediating the gene expression of a large array of proinflammatory genes, and consequently the release of soluble mediators (cytokines, chemokines) and cellular components (e.g. tumor-associated macrophages), promoting cancerogenesis.[16]

Chronic inflammation results in the formation of typical risk factor lesions in epithelial prostate cells, called 'proliferative inflammatory atrophy' (PIA). These lesions occur predominantly at the periphery of the prostate gland, where PC typically arises. Many of the PIA areas may show morphologic transitions in prostatic intraepithelial neoplasia (PIN) lesions considered putative PC precursors by ***De Marzo et al.*** By examining serial sections of whole-mount prostates from 50 cases, they observed that 17% of PIN lesions were found to be

in the morphologic process of merging with PIA in 70% of the prostates examined.[11]

In addition, an increasing number of recent histologic investigations confirm that PC tissues are commonly characterized by chronic inflammation. Lymphocytes, macrophages and, less frequently, other plasma cells and eosinophils were commonly observed in the tissue samples. In particular, they showed increased infiltration of CD45+ cells in PIA lesions (all leukocytes express CD45 and non-leukocytes do not) with 70–80% of CD3+ T lymphocytes and10–15% of CD19+or CD20+ B cells. Macrophage numbers also seemed increased in PIA lesions.[17]

During PC development and progression, the role of innate/inflammatory immune cells is also crucial. It has been demonstrated that activation of the innate immune response (particularly through the NF-κB pathway) through Toll-like receptor4 (TLR4) -mediated recognition of pathogen-associated molecular patterns or damage-associated molecular pattern molecules can promote tumor development. This results in a milieu rich with inflammatory mediators. Thus, inflammatory mediators released through the NF-κB-TLR4 pathway may contribute through their physiologic functions to the development and progression of cancer, such as PC.[18]

Studies indicate that TLR4-mediated inflammation induced from bacterial and viral infection or from other

endogenous and exogenous agents can promote the development of cancers, such as PC. Thus, the blockade of signaling pathways required for inflammation or the induction of proinflammatory mediators might decrease the risk of tumorigenesis. Several agonists have been developed as anticancer drugs. Accordingly, the combination of peptide-based vaccines with TLR agonists may greatly improve the therapeutic potential of cancer vaccines.[19]

Study of the human genome has enabled the dissection of complex human traits and has paved the way to understanding the basic pathways of health and disease. The large majority of genetic variants studied are SNPs that occur with a frequency of >1% in the normal population (in contrast to 'mutations' that occur with a frequency of <1%). Three genetic epidemiologic approaches (the candidate gene approach, pathway analysis, and genome-wide association studies) have been used to assess SNPs of proinflammatory genes and PC risk. In addition, the number of studies reporting on the association between one or multiple SNPs in inflammation-related pathways, and thus PC risk, has greatly increased.[20]

The candidate gene approach is a hypothesis-driven method that is widely used. Sequence variants of several inflammatory genes have been extensively explored to predict PC risk, even if most of these findings are inconsistent. However, some interesting data have been obtained. Among these, an interesting association has been observed by ***Licastro***

et al. between an SNP (GG genotype) in the promoter region of α-1-antichymotrypsin and increased risk for PC.α-1-Antichymotrypsin is an acute-phase protein upregulated in response to inflammation. α-1-Antichymotrypsin is also a serine protease inhibitor, and most circulating PSA is bound to Antichymotrypsin.[21]

Another recent case–control study in the risk factors for PC study, by examining a cytokine-rich region at 5q31.1 observed a modest association between two alleles of IL-4 and PC risk and no association between IL-5 or IL-13. The associations with IL-4 were not present in another large case–control study (the Melbourne Collaborative Cohort Study). However, one of the IL-4 alleles (rs2243250 genotype) led to a decrease in IL-4 activity, potentially pointing to an antitumor function of IL-4 in PC risk.[22]

Other inflammatory molecules seem to have a crucial role in PC. Among these, COX-2 (also known as PTGS2). This enzyme is an inducible isoform of the enzymes that convert arachidonic acid to proinflammatory prostaglandins. An overexpression of COX-2 in PC has been observed, particularly in PIA areas.[23]

Strong correlation noticed between genetic variants of genes of the TLR4 pathway and PC susceptibility in humans. In particular, a large number of recent case–control studies performed in different populations of the world have examined

the role of TLR4 SNPs in PC. ***Cheng et al.*** analyzing six TLR4 SNPs in 1012 men, demonstrated that rs10759932 SNP was associated with a fourfold increased risk of disease.[23]

Of the other TLR4-related pathway genes, only some SNPs of CD14 and NF-KB1genes have been analyzed to evidence their ability to modulate PC risk. In particular, the CD14 polymorphism, located near the Sp1 transcription factor binding site and known to have a major influence on CD14 expression, has been demonstrated to be associated with PC in old African-American men in a study including 264 cases and 188 controls. Furthermore, a functional insertion/deletion polymorphism (e94 insertion/deletion ATTG) in the promoter of the NF-KB1 gene has also been genotyped in a total of 117 PC patients and 143 control subjects. The frequency of the ATTG2 allele in PC patients was significantly higher than in controls (63.7% vs 54.5%). Thus, the functional NF-KB1 promoter polymorphism seems to be associated with increased risk for PC.[24]

An overexpression of TLR4 and endogenous TLR4 ligands has been observed in PC cells. However, TLR4 engagement by endotoxin and by endogenous ligands represents a notable contribution to the outcome of different cancer treatments, such as radiation or chemotherapy.[25]

In the post-genome era, a genome-wide association study has become a powerful tool for analyzing the whole genome

and identifying SNPs related to the outcome of interest. Several genome-wide association studies have recently identified more than 40 germline variants of various genes or chromosomal loci that are significantly associated with PC susceptibility, including multiple 8q24 loci, prostate-specific genes, metabolic- and hormone-related genes and many regions where no coding gene is annotated. However, there are only a few variants or genes for which biologic significance or functions have been elucidated so far. The greatest challenge related to genome-wide association studies-associated loci in prostate genomics is to understand the functional consequences of these PC-associated loci and their involvement in PC biology and carcinogenesis.[26]

There have been attempts to determine PC risk estimations by combining multiple PC-associated variants for clinical tests, and these can identify a very minor population with a high risk for PC. However, they cannot distinguish the risk for aggressive PC from that for non-aggressive PC. Further identification of PC-susceptibility loci in larger genome-wide association study cohorts and biologic insights gained from such functional analyses have the potential to translate into clinical benefits, including the development of reliable biomarkers, risk estimation and effective strategies for screening and prevention of PC.[27]

Sex steroid hormones are assumed to have a critical role in the complex pathophysiology of human PC. Androgens are

primarily responsible for the development and function of the human prostate gland as well as for the maintenance of homeostasis of prostate tissues in adulthood. The major prostatic androgen is testosterone and its derivative di-hydrotestosterone (DHT), produced locally through the 5α-reductase enzyme. Most of their effects are mediated by binding to androgen receptors (AR). Androgens also represent well-established risk factors for development and progression of benign and malignant disorders of the prostate gland.[28]

Current evidence also suggests a crucial role of estrogens in both normal and diseased human prostate. In particular, it hypothesizes that a combined action of androgens and estrogens and their balance seems to be remarkable in maintaining prostate health and tissue homeostasis. An alteration of this balance has been evidenced to be involved in the development of both benign and malignant diseases, including PC.[29]

In aging men, circulating levels of estradiol are unchanged or increased, as opposed to the decline of plasmatic testosterone. Estrogen production is maintained through aromatization of adrenal androgens driven by the aromatase enzyme, especially in peripheral adipose tissue. In normal prostate gland, the aromatase enzyme is expressed within the stroma, while the malignant prostate shows an aberrant aromatase expression in the epithelial compartment. This has been associated with an increased risk for PC.[30]

This condition is further complicated by the differential expression and activity of the two estrogen receptors (ER), α and β. A sustained activation of ERα may eventually lead to an aberrant proliferation, inflammation and to the development of premalignant lesions. In contrast, ERβ receptors have antiproliferative effects and exert a protective role against prostate carcinogenesis**.** Despite the above evidence, many epidemiologic studies have failed to show a significant association between circulating sex steroids and PC risk. In particular, SNPs of genes involved in both metabolism and action of steroid hormones seem to be primarily implicated.[31]

MicroRNAs (miRNAs) are small noncoding RNAs that take part in post-transcriptional regulation either by arresting the translation or by cleavage of mRNA targets. MiRNA regulation is performed by pairing the miRNA to sites in the messenger RNA of protein coding genes. miRNAs have been thought to be involved in many biologic processes (i.e. cell proliferation, death and differentiation) and are believed to regulate the expression of approximately one-third of all human genes. Mature miRNAs bind to their target miRNAs by complete or incomplete complementation of their 50-end nucleotides 1–8 (seed sequences) with a binding site in the 30- or 50-untranslated regions of target transcripts or in the coding sequences. This process results in direct cleavage of the targeted mRNAs or inhibition of translation. Currently, nearly 1700 human miRNAs have been identified.[32]

Chapter Two

MANAGEMENT OF ADVANCED PC

ADT usually with the use of a single-agent luteinizing hormone-releasing hormone (LHRH) agonist or by surgical castration—is the standard approach for first-line treatment of patients with advanced PC. [33]

ADT refers to any intervention which results in the ARof target cells not being activated by either a reduction in the production of testosterone or blockage of the androgen receptor. This treatment approach is achieved via both surgical or medical castration, anti-androgen therapies, and any combinations of these. The aim of castration is to decrease serum testosterone to 50 ng / dl such that the stimulation of PC cells is minimized. In clinical practice 20 ng / dl are usually reached. Surgical castration by bilateral orchiectomy (BO) has been recognized as an effective method of rapidly decreasing testosterone levels since the 1940s.[34]

BO is a quick and simple procedure with little surgical risk. The testes typically produce about 95% of the testosterone level in men and BO rapidly decreases the serum testosterone concentration to castrate levels within 3–12 h. However, in the United States, orchiectomy is used as initial therapy in only 7–27% of men with metastatic PC, likely because of the psychological impact of surgical castration on men.[35]