Personalized Therapy of Prostate Cancer

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REVIEW

Personalized Therapy of Prostate Cancer

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ABSTRACT

As prostate cancer is the second leading cause of death after lung cancer, several diagnostic strategies have been introduced in recent years. Among these prostate-specific antigens, it is widely recognized that this is the simplest and most common clinical endpoint - genetic instability is part of the oncogenic process. Gene mutations involved in DNA repair mechanisms may promote this genetic instability and participate in oncogenesis and metastatic progression. In prostate cancer, abnormalities in DNA repair are primarily due to somatic or constitutional mutations in the BRCA1/2 genes. Treatment options for prostate cancer are currently widely discussed in the media and by urological associations. Focal therapy is expected to have the same oncological efficacy as whole gland therapy with fewer side effects. Accurate diagnosis with multiparametric magnetic resonance imaging (MRI). In this review we examine the various studies described the molecular targets for personalized prostate cancer therapy.

KEYWORDS: Prostate Cancer; PSA; BRCA1/2; Personalized Therapy.

INTRODUCTION

Personalized medicine emerges to apply the right treatment at the right time to each individual by seeking for his characteristics such as genetic profile. It use a lot of resources in order to find the right diagnostic, prognostic and predictive [1]. Individualized medicine had already demonstrate her efficacy in such specialties, like measuring... disease, we will furthermore understand how personalized medicine treat the prostate cancer[2], we will focus on the application of personalized medicine in cancer, particularly in prostate cancer.

Commonly, prostate cancer (PC) cause a significant amount of men’s death in western societies, and it's the most spread type of adult malignancies in the whole world [3]. PC is a heterogenous disease at both the clinical and molecular level; however, the agents causing the onset of prostate cancer are unknown. A small number of risk factors have been identified (Age, Endogenous hormone balance, Genetic (predisposing) factors and Environment factors), although they are supported by a large number of small studies, leading to contradictory or inconclusive results[4]. To choose the appropriated therapeutic option, evaluation of life-expectancy is essential to offer an optimal individualized treatment. It is essential to take into account the patients’ aspirations before starting any diagnostic and therapeutic approach (Mongiat-Artus and Avenin 2017). The objective of our current review is to present the molecular targets for personalized prostate cancer therapy.

INCIDENCE AND MORTALITY

According to data from general cancer registries, grouped by Francium [5], the incidence is increasing regularly every year, an annual increase in incidence of 7.9% was noted between 1995 and 2000 (Figure 1). Incidence increases with age; the risk to get PC before age 50 is very low (0.3%) [6].The median age at diagnosis is declining to 70 years in 2004 old as compared to 74 years old in 1995 [7], with 10,004 deaths in 2000. The PC death rate increases by 0.17% per year. The increase of deaths number is explained mainly by the ageing of the population [5].
PROSTATE-SPECIFIC ANTIGEN (PSA)

PSA, also renowned as kallikrein-3, is a glycoprotein developed by the prostate. Its function is to liquefy the serum and promote sperm movement and dissolution of cervical mucus. PSA was uncovered by Richard Ablin in the 1970s; according to his conclusions, it then led to "Catalona et al. (1991) recognized the possibility of early detection of PC. Reported a group of 1,653 men who underwent a PSA test in addition to a digital rectal exam.[8]; PSA is the most abundant protein in seminal fluid; concentration of PSA in the seminal fluid was 1000 times higher than its concentration in serum. It has a low molecular weight protease composed of 240 amino acids [10]. Protein dosage enable PC detection, but several aspects must be considered [9] the threshold value of 4 ng/ml is conventionally used. A value threshold for total PSA < 4 ng/ml is proposed for ages less than 70 years or for at-risk groups. The threshold of 3 ng/ml is commonly used in screening protocols [7]. The PSA dosage has upset the management of PC at all stages of development. PSA supplies prognosis at all stages of the PC, both before and after treatment, regardless of the treatment chosen. The PSA simplified the initial extension assessment and monitoring.[9]

The prescription of PSAT for early detection has made which has been the subject of much criticism. In contrast, the authorities most opposed to its use have returned to the issue. Their restriction due to new data including new therapeutic targets. Next generation sequencing analysis advances in the treatment of castration-resistant PC (CRPC), options remain limited and incurable. PC rests one of the most deadly cancers in men. The discovery of new therapeutic targets is necessary to improve the result of men with metastatic PC. Precision/personalized medicine has produced innovative prospects to discover therapeutic targets. Next generation sequencing analysis increases the identification of potential relevant tumor mutations [16].

BRCA1 AND BRCA2 MUTATION

BRCA1 was firstly Jewish Breast Cancer Patients and Frequency The overall distribution of Ashkenazi Jews is ~1%. This variant was also found in non-Ashkenazi, Spanish and British Jewish communities. For PC, BRCA2 is significantly associated with an increased risk PC of Ashkenazi Jews. In a large-scale controlled study, 251 unselected Ashkenazi PC and 1,472 healthy control men were recruited [12]. The presence of BRCA1 / 2 mutations is related to the presence of mutation characteristics associated with HR deficiency in adenocarcinoma of the prostate. The HRD profile has also been detected in some patients without gremlin or somatic mutations in BRCA1 / 2 / other HR-related genes. This is likely to define a subset of PC patients accurately identified by the WGS data, and these patients are likely to benefit from PARP inhibitors or platinum therapy [13]. The presence of BRCA1 / 2 mutations is related to the presence of mutation characteristics associated with HR deficiency in adenocarcinoma of the prostate. The HRD profile has also been revealed in some patients without gremlin or somatic mutations in BRCA1 / 2 / other HR-related genes. This is likely to define a subset of PC patients accurately identified by the WGS data, and these patients are likely to benefit from PARP inhibitors or platinum therapy [14]. Among BRCA mutation carriers, the risk of PC is 1.90 times higher. This increased risk of PC is primarily attributed to the 2.64 times higher risk of BRCA2 carriers, and the risk of PC in BRCA1 carriers is 1.35 times higher. The frequency of the BRCA2 mutation in PC patients is higher than BRCA1 mutation. BRCA2 mutations are the most associated to PC mortality. BRCA mutations can stratify high-risk patients and guide clinical strategies to more effectively treat patients with DCP [15]. Despite advances in the treatment of castration-resistant PC (CRPC), options remain limited and incurable. PC rests one of the most deadly cancers in men. The discovery of new therapeutic targets is necessary to improve the result of men with metastatic PC. Precision/personalized medicine has produced innovative prospects to discover therapeutic targets. Next generation sequencing analysis increases the identification of potential relevant tumor mutations [16].

PERSONALIZED MEDICINE

In the field of health, nothing better than so-called personalized medicine to illustrate the general debate on the impact of invention. Faced with the marketing commitments linked to the commercialization of certain biomarkers, "make every therapy a therapy". "Unique", scientists have the right to recall that so-called personalized medicine does not literally mean creating unique and personalized medicines and treatment procedures for each patient, but the ability to classify...
individuals into subgroups sensitive to infection or response for specific therapies [17]. The use of biomarkers in oncology may guide to benefit from more effective and less toxic cancer treatments. The rise of molecular biology has brought about dramatic changes in the development of targeted molecular therapies [18]. These two genes play a key role in the repair of double-stranded DNA through homologous recombination, a faithful repair mechanism. If the function of the gene is lost, the cells are deficient homologous recombination and genetically unstable, this sensitivity can be used in certain targeted therapies. The lethality principle describes a situation in which a defective gene is compatible with cell survival, but it is combined to a second defect. It causes cell death as described by Hartwell et al in therapeutic targeting of tumors. So far, although ovarian cancer has been widely studied in PC. In practical applications, ovarian cancer has been the main focus of synthetic lethal research [19]. However, there are an obstacles to overcome. The molecular profile of a tumor is not a substitute for histology, as demonstrated by the lack of clinical benefit seen in the SAFIR-01 and SHIVA tests. The functional impact of many mutations remains unknown. The complexity of interpreting genomic profiles is influenced by the tumor purity of the sample, detection thresholds, or available libraries, which complicate to overcome in order to identify the real drivers of oncogenic and overcoming treatment resistance. Epigenetics presents a novel track to explore, an additional however unavoidable dimension for the understanding of tumor biology [20].

CONCLUSION
In recent years, active surveillance has been proposed as the standard for PC management. Prostatectomy, although less performed few years ago, is now mainly performed with robotic assistance and although the level of evidence is controversial. Its worldwide use is based on undeniable ease of use. Finally, between active surveillance and validated conventional treatments for PC (total prostatectomy, brachytherapy and radiotherapy) there is certainly room for care may be more acceptable to patients than active surveillance and less morbidity than conventional treatments and represents a focal treatment. In contrast, pending the results of randomized trials, supervision of focal treatment practices is necessary[21].Neither neo adjuvant treatment has exposed a benefit by terms of progression-free survival, specific or overall survival, but the question deserves to be asked again for high-risk and locally advanced tumors with new hormonal treatments[6].

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