Prognosis of Prostate Cancer and Tumor Heterogeneity

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Prostate cancer (PCa) is a highly heterogeneous complex cancer that shows widely varying levels of mortality and morbidity. Among PCa cases, adenocarcinomas that have an acinar origin have a far better prognosis than those with a ductal origin. Localized PCa is often found to be morphologically heterogeneous within the same patient. Multiple tumor foci can appear within the prostate organ (intertumoral heterogeneity), and they can have genetic differences that cause various degrees of metastatic spread and treatment resistance.

prostate cancer PSA resistance mutation

1. Introduction

The prostate, which is an accessory reproductive organ in men, is located below the bladder. Its major function is to complement the essential secretions to semen and to keep the sperm viable. The adult human prostate is divided into central, transitional, and peripheral regions. More than 95% of prostate cancer (PCa) cases are adenocarcinomas, most of which have an acinar origin, while few have a ductal origin. Almost 80% of prostate adenocarcinomas arise from the luminal or the basal (with a lesser prevalence) epithelial cells in the peripheral regions, which occupy >70% of the total prostate tissue. The prevalence of PCa in men who are aged >65 years is approximately six out of ten cases. It is more frequent among Caribbean men of African ancestry and among African American men than among men of other races; however, the reason for this remains unclear. Due to its high prevalence, PCa is the second most diagnosed solid-organ cancer, after lung cancer, in men [1][2] and it is also a major health issue, with 358,989 identified deaths globally and approximately 1.3 million newly diagnosed cases in 2018 [3]. Worldwide, approximately 10 million men are currently living with the disease, and approximately 700,000 of them have a metastatic form of the disease [4]. Although PCa is generally diagnosed at an early stage, the risk–benefit ratio of the treatment remains uncertain. It is one of the most disputed areas of medicine because of the significant morbidity from the current form of therapy [5][6]. Because of its long disease history and uncertainty in individual patients' clinical progress, clinicians tend to consider the treatment workup of PCa as a long journey [7].

PCa is a heterogeneous disease that shows a wide variability in biology and clinical progression. Estimating the degree of risk based on clinical features and distinguishing low-risk localized PCa from aggressive PCa are the central clinical challenges that must be overcome in order to further improve outcomes while adapting the treatment to individual risk profiles and the risk of PCa-specific morbidity and mortality. The global men's health

charity “Movember” commissioned a formal landscape analysis in order to evaluate the current PCa research field and reported 17 research needs [8].

2. Prognosis of Prostate Cancer

PCa is a highly heterogeneous complex cancer that shows widely varying levels of mortality and morbidity. Among PCa cases, adenocarcinomas that have an acinar origin have a far better prognosis than those with a ductal origin. Approximately 80% of men who are diagnosed with PCa are diagnosed with prostate-limited localized PCa [9].

If it is diagnosed at an early stage, the life expectancy for men with localized PCa can be as high as 99% for more than 10 years [10]. For most men with PCa, managing a customized treatment plan for a slow-growing, and often even indolent, cancer is necessary in order to live with the disease; however, for several others, relapsed PCa following a definitive treatment plan may be aggressive and, in unusual cases, may be unresponsive to the current form of standard care. Approximately 5% of men who are diagnosed with PCa are diagnosed with distant metastases (often in multiple sites), and 15% of them are diagnosed with locoregional metastases [9]. If they are diagnosed with late-stage PCa (distant metastases), men have a poor overall survival rate of only 30% for five years [9]. Metastatic PCa accounts for more than 400,000 deaths annually, and it is expected that this mortality rate will increase by two-fold or more by 2040 [4]. Moreover, it is estimated that, after diagnosis, a similar number of men will live with treatment-related morbidity for more than 10 years [4]. The metastasized PCa cells can stay dormant in the tumor microenvironment at a secondary site for a long time. The metastasis of PCa is primarily associated with the spread to the locoregional lymph nodes and/or the hematogenous spread to the stroma of the bone marrow in the axial skeleton [11]. More than 80% of distant metastatic lesions are found in the bone tissue [11]. In more unusual cases, the metastasis of PCa is associated with the spread to distant visceral sites. Almost all patients with metastatic PCa ultimately experience castration-resistant PCa (CRPC), which is refractory to androgen deprivation therapy (ADT). These features are the principal causes of PCa morbidity and mortality [11]. Metastatic CRPC (mCRPC) eventually becomes therapy- and castration-resistant PCa (t-CRPC), which has no further effective solution and is considered to be an end-stage disease [12][13].

3. Tumor Heterogeneity

Localized PCa is often found to be morphologically heterogeneous within the same patient. Multiple tumor foci can appear within the prostate organ (intertumoral heterogeneity), and they can have genetic differences that cause various degrees of metastatic spread and treatment resistance [14]. The genomic heterogeneity that can be observed in localized PCa confronts the concept of a “dominant cancer lesion”, which can be largely responsible for a patient’s clinical course. Furthermore, the cancer cells within one focus may arise from different ancestor cells that become individually transformed [15] or from one single clone that transforms and diverges into multiple distinct clones in one focus (intratumoral heterogeneity) [16]. The metastatic PCa that often occurs in multiple locations and is supposed to be clonally derived can harbor multiple subclones that are genetically distinct with different molecular features [17].

The heterogeneity of potential cancer driver genes further complicates the understanding of the clinical profile of PCa at the time when it is diagnosed and the treatment options with the available targeted agents in the future. In the prostate epithelial cells, differentiation and proliferation are dependent on the androgen receptor (AR) activity, and current ADT takes advantage of the PCa's dependence on the AR activity. ADT and second-line therapies are also believed to increase the heterogeneity [18]. The role of tumor heterogeneity is suspected to be in the progression of PCa during or after standard ADT. Molecular heterogeneity indicates that the genomic features may determine the disease severity and the unresponsiveness to conventional therapy [19]. Current diagnostic prostate biopsy is significantly hampered by this polyclonality, because one large biopsied lesion does not always provide sufficient insights into the other lesions.

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