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Review

Applications of circulating tumor cells for prostate cancer

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Abstract One of the major challenges that clinicians face is in the difficulties of accurately monitoring disease progression. Prostate cancer is among these diseases and greatly affects the health of men globally. Circulating tumor cells (CTCs) are a rare population of cancer cells that have shed from the primary tumor and entered the peripheral circulation. Not until recently, clinical applications of CTCs have been limited to using enumeration as a prognostic tool in Oncology. However, advances in emerging CTC technologies point toward new applications that could revolutionize the field of prostate cancer. It is now possible to study CTCs as components of a liquid biopsy based on morphological phenotypes, biochemical analyses, and genomic profiling. These advances allow us to gain insight into the heterogeneity and dynamics of cancer biology and to further study the mechanisms behind the evolution of therapeutic resistance. These recent developments utilizing CTCs for clinical applications will greatly

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impact the future of prostate cancer research and pave the way towards personalized care for men.

1. Introduction

Prostate cancer (PCa) remains one of the most prevalent cancers affecting men across the globe. In 2012, PCa was the second most common cancer in men with more than 1.1 million new cases, accounting for around 8% of all new cancer cases and 15% in men. It was also noted to be the fifth prominent cause of cancer-related mortalities in men globally with more than 307,000 deaths [1].

The understanding of PCa biology has been advanced with tremendous amount of data from molecular studies, generating new classification schema [2,3], and prognostication tools [4] that go beyond the Gleason grading and TNM staging systems. It is anticipated that these advancements will reshape our therapeutic approaches for PCa. Tissue samples taken during prostatectomy and core needle biopsies are now being utilized for molecular profiling, driving many of these advances. These specimens provide information representing historic and often untreated cancers. There have also been autopsy series that have shown a very different molecular portrait of PCa and in particular, metastatic-castration resistant PCa (mCRPC). Profiling from these autopsies has provided further insight into the temporospatial heterogeneity that underlies advanced cancer. This has raised questions about the dynamic and evolving biology of mCRPC in the interval between diagnosis and death, which is currently under investigation in centers where tissue-oriented studies have been conducted. The typical clinical practice in caring for men with PCa has not involved routine tissue biopsies. This poses a challenge for translational research efforts as such material is needed to conduct molecular characterizations over time. The challenge in obtaining metastatic tissue samples in mCRPC mainly lies in its typically osteotropic nature resulting in the formation of osteoblastic lesions. The vast majority of patients are not inclined toward having serial bone biopsies which may require specialized instrumentation such as drills to cut through osseous metastases. Additionally, sampling viable tissue samples from osteoblastic lesions requires experienced interventional radiologists with specialized expertise in obtaining samples from bone and other sites that are useful for analysis. Even with the highest levels of expertise, these methods will tend to yield usable samples in only 60%—70% of cases. Finally, the process of removing or decalcifying pieces of bone from biopsies or bone marrow aspirates, places relevant and important information about the tumor at risk for loss or deterioration.

In contrast to this, blood analysis has been a standard of practice in this clinical setting. Clinical phlebotomy is simple enough that frequent blood draws can be used to measure changes in serum prostate specific antigen (PSA) concentration. For decades, serum PSA concentration has been utilized to monitor the therapeutic efficacy of various interventions including surgery, chemotherapy, androgen-receptor (AR) inhibition, and radiotherapy. It is known, however, that changes in PSA do not predict clinical benefit for other types of treatments such as immunotherapy and targeted radionuclide therapy. Decisions made solely based on serum PSA concentration changes early on in therapy when patients are clinically well are cautioned against in the recommendations provided by Prostate Cancer Working Group 3 [5]. Nonetheless, it is apparent that blood-based observations of PCa patients can be readily obtained, which has led to greater interest in developing similar tests that could complement PSA measurements and overcome some tumor biopsy limitations [6,7].

The unmet need for new blood-based tests also stems from the restrictions in monitoring anaplastic or atypical carcinomas in the prostate gland, which have absent or low levels of PSA production. A distinctive feature common to these aggressive variants, is the potential for developing visceral metastases (VM), which often times progresses rapidly and lead to end organ failure and death. It is widely recognized that serum PSA measurements lacks predictive capacity in many mCRPC cases with VM, which tend to be less dependent on AR activation and are more resistant to conventional AR-targeted therapies [8—10]. In addition to this limitation, routine monitoring of metastases in soft tissue organs is conducted far less frequently in PCa patients, which leads to later diagnoses of VM events. This is further complicated by the observation of an increasing incidence of VM events that coincides with the more frequent and early use of potent AR-inhibitors [8]. Thus, a blood-based tool capable of monitoring the behavior of these cancers would be an ideal way to address this unmet need.

Circulating tumor cells (CTCs) may provide an important means of addressing the limitations facing clinicians caring for men with PCa. CTCs are a rare population of tumor cells that circulate in the blood stream after detaching from a primary tumor and/or metastatic lesions. Compared to the 10 hematologic cells found in 1 mL of whole blood [9], there are usually less than 100 CTCs found in the same blood volume [11—13]. This creates challenges in conducting molecular characterization of CTCs. In order to address this issue, numerous methods and technologies have been developed for isolating and studying CTCs. These initiatives are uniting the basic and clinical sciences together allowing for the possibility of real-time dynamic profiling of disease progression and better care for PCa patients.

2. Early clinical application of CTCs: enumeration

In 2008, the FDA cleared the CellSearch™ System (Veridex) for the enrichment and enumeration of CTCs in mCRPC

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