Biomarkers in Medicine


(doi:10.2217/bmm.11.42)

The need for personalized therapy and companion diagnostics in prostate cancer

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It has become widely accepted that further progress in the treatment of many diseases, including cancer, are requisite of a personalized approach to healthcare (i.e., personalized medicine).

Worldwide, prostate cancer (PCa) is the second most commonly diagnosed cancer in men, with approximately 899,000 new cases and 258,000 deaths in 2008 [1]. An increasing number of members of the biomedical community have finally come to the realization that effective clinical management of PCa has been hampered on the one hand by significant intra-tumoral heterogeneity on the genomic and pathological levels, and on the other hand, by the limited understanding of the genetic elements governing the progression of disease. This is perhaps best exemplified by the rather substantial recurrence of disease following traditional treatments such as radical prostatectomy and radiation, not only with their associated morbidities, but also the subsequent development in many patients of advanced hormone-refractivity and metastatic disease. Indeed, not withstanding improvements that have recently been made (e.g., with cabazitaxel), most commonly used chemotherapeutic agents have had little or, at best, a transient effect.

The foregoing considerations reflect the impact of individual phenotypic variations in PCa detection and treatment. Not only do we need to develop new methods and/or agents for the treatment of PCa, but also individualized treatments – personalized medicine. One treatment does not fit everyone. This individualized approach to PCa detection and treatment must include companion diagnostics (i.e., a biomarker/target) and bioanalytical methodology to provide biological and/or clinical information, to guide development and use, and to assess whether a patient will respond favorably to a specific treatment [101].

In looking forward by looking backward, initially, prostate-specific antigen (PSA), although not cancer specific, has been used as a cancer marker for diagnosis, prediction of PCa risk and monitoring the response to treatment. In the latter case, PSA serves well as a harbinger for recurrence of disease. However, many have been slow to recognize that the use of PSA for screening lacks sensitivity and specificity, and cannot distinguish an aggressive from a nonaggressive cancer, thereby leading to overdiagnosis and overtreatment [2].

In view of the shortcomings of PSA, numerous tissue, cell and genetic alterations associated with PCa continue to be found [3]. However, no biomarker has been identified to overcome the limitations of PSA and change the current standard of care of treating PCa [4]. However, within the past year, there have been a number of very promising biomarkers and modulators of tumor growth and invasiveness identified. These include a four-gene signature, with SMAD4 as the key regulator [5], SPINK1 [6] and cell cycle proliferation genes [7] prognostic of growth and metastatic progression, and the promising,
but currently presumptive role of prostate transglutaminase, which is reviewed in this issue [8]. In addition, investigating the metabolite content of cancer cells, the metabolome–sarcosine has been identified as a biomarker of PCa progression [9]. These genes are representative of endeavors toward personalizing treatment of PCa.

With the foregoing explanation of the need for personalized medicine for the treatment of PCa and general considerations by Ross [10] of some of the concerns en route toward achieving this, irrespective of the disease, one possible approach is immunotherapy.

The immune system has exquisite sensitivity and specificity, and has traditionally held promise for irradicating, if not controlling, cancer locally and systemically, sparing normal tissue and with minimal sequelae. Furthermore, the immune response may leave behind a long-term memory serving to protect the patient from subsequent disease. Presently, to my knowledge, there is no treatment regimen for cancer that can claim such specificity of memory.

In the case of PCa, there are several factors implicating the role of tumor–host interaction in its pathogenesis and, therefore, of the immune system, and excellent possibilities of personalized therapeutic intervention [11]. These factors include:

- Wide variation in the age of onset of clinical disease;
- High incidence of occult foci (asymptomatic cancer) found on routine autopsy;
- Immunogenicity of prostate tissues and secretions;
- Demonstration of humoral- and cell-mediated immunity;
- Localized induced immunologically mediated destruction of the prostate following immunization;
- Regression of metastasis following immunization.

In addition, it has been recognized that the immunological characterization of a patient’s immune status (i.e., ‘immunostaging’) and elimination of immune tolerance by a variety of immunosuppressive factors will be beneficial toward facilitating an effective anti-tumor immune response [11].

The first phases of the reality of immunotherapy as a personalized approach to PCa may be witnessed by the recent US FDA approval of an autologous vaccine Sipuleucil-T (Provenge®), and other immunological strategies in clinical development [12]. These include trials of the use of a novel approach toward interruption of immune tolerance with the antibody ipilimumab [12].

As has been very well stated by Ross, “The realization of the integration of diagnostics with therapeutics and the transition to personalized medicine are not without challenges” [10]. The comments and recommendations in this article have been made as possible steps toward meeting the challenges in the case of PCa and hopefully improving the current standard of care – long overdue for this malignancy.
Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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(Accessed 28 April 2011)

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