Personalized Medicine in Metastatic Castrate Resistant Prostate Cancer: Do We Still Have to Treat Everyone the Same Way?

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Stratified Medicine: Matching the Right Patient with the Right Therapy

The recent successes in phase III clinical trials for metastatic castrate resistant prostate cancer (mCRPC) [1-6] has led to increased optimism in our ability to treat this aggressive disease. However, as our experience with these new agents matures, we face a challenge in deciding which approach will work best for which patient. The advent of personalized medicine has begun to address this challenge, allowing a stratified medicine-based approach to select particular patients for particular treatment approaches. Thus, amplification of the erbB2 oncogene, as measured by fluorescence in situ hybridization (FISH), allows selection of the 30% of breast cancer patients who overexpress erbB2 and who would benefit from treatment with the monoclonal antibody trastuzumab (Herceptin; F. Hoffmann-La Roche, Basel, Switzerland) [7]. Detection of the wild-type Kirsten ras gene (KRAS) by mutational analysis identifies the subgroup of colorectal cancer patients who will respond to treatment with cetuximab [8], while the presence of an anaplastic lymphoma kinase (ALK) rearrangement in a proportion of non-small cell lung cancer (NSCLC) patients has underpinned the development of the ALK inhibitor crizotinib as a new standard of care for those patients [9]. We can also use the same principle to spare those patients who will not respond from the side effects of a toxic therapy.

Predictive Biomarkers In mCRPC: The Holy Grail?

A common theme for each of these examples of stratified medicine is the use of predictive biomarkers in selecting subgroups of patients for particular therapies. So do we have similar tools to facilitate decision making in mCRPC? While prostate cancer is molecularly highly heterogeneous, some common molecular lesions are present in the disease, including PTEN loss, mutations affecting the PI3-kinase pathway, and TMPRSS2/ERG rearrangements [10]. However, to date, there is little evidence to suggest that any of these molecular changes predict response to therapy. A recent study of TMPRSS2/ERG rearrangements as part of the COU-AA-302 trial (abiraterone acetate in mCRPC with no previous chemotherapy) [5] suggested a potential association between the 2+ EDel variant and greater benefit from abiraterone [11].

It is important to remember that molecular predictors are “the new kids on the block,” and their current status in prostate cancer is disappointing. So can we use clinical factors as predictors of response to different treatments? Evaluation of preplanned subgroup analyses of a number of the trials outlined above, using criteria such as “presence of pain” or “visceral metastases,” does not reveal any clear clinical indicators [1, 2, 4, 5], although they may underpin the generation of valid hypotheses for future testing. In addition, while distinct clinical indicators may not permit treatment stratification, they may provide some insight about when to treat and also inform the sequence of treatments in combination approaches.

One area in biomarker development in mCRPC that is showing promise is detection and interpretation of circulating tumor cells (CTCs) [12]. While most of the research on CTCs in mCRPC to date has focused on their use prognostic markers [13, 14] or response surrogates [15], they may also have relevance in disease subtype classification to guide treatment selection [16]. The CellSearch® assay (Veridex LLC, Raritan, NJ) is the only CTC-detection platform currently validated by the FDA for patient use, although its true value in guiding treatment decisions remains unproven.

Predictive Biomarkers: The Need For A Rigorous Framework

A rigorous approach must be employed in the identification and validation of predictive biomarkers, be they molecular or clinical. The development of a new framework for clinical trials in CRPC by the Prostate Cancer Working Group (PCWG2) in 2008 [17] included the establishment of robust criteria for both analytical and clinical validation of a predictive biomarker for its use in informing the clinical decision-making process [16].
Personalized Medicine In mCRPC: Bridging The Gap

The significant improvements we have seen in the management of mCRPC in recent years gives great cause for optimism. We now have a number of active drugs that can improve symptoms, quality of life, and survival. The challenge is to decide how best to use these agents, in which patients, and in which order. In order to answer these questions, we may need to identify predictive markers that can be used with confidence in the individual patient. Only then will the promise of personalized medicine for mCRPC be truly within our grasp.

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