The path forward in prostate cancer therapeutics

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The last decade has seen remarkable advances in the treatment of prostate cancer. Until 2010, only docetaxel had demonstrated the ability to improve the survival in metastatic castration-resistant prostate cancer (mCRPC).1 While effective, many men were reluctant to get treatment with docetaxel because of the perceived toxicity, thereby further limiting the benefit of the one available and effective therapy. Remarkably, within the last 8 years, the field has seen a multitude of therapies that demonstrate an ability to extend survival for men with prostate cancer. Abiraterone and enzalutamide demonstrated the importance of the androgen axis in propelling prostate cancer growth.2 3 Sipuleucel-T was immunotherapy’s entry into the evolving prostate cancer armamentarium, as the therapeutic cancer vaccine established an ability to extend survival despite an apparent lack of short-term effect on progression-free survival and prostate-specific antigen (PSA).4 Radium-223 built on the palliative success of previous radiopharmaceuticals, but this alpha-emitting agent importantly had a minimal hematologic-related toxicity and was associated with a survival advantage, unlike its in-class predecessors.3 Cabazitaxel also emerged as a second-line chemotherapy option in patients who had already progressed on docetaxel.6

More recent data have also verified that using some of these agents (docetaxel and abiraterone) earlier (in patients with metastatic castration-sensitive prostate cancer), the clinical impact and survival timelines can be substantially improved. With this stunning series of therapeutic successes having now crested for the time being, important questions remain for the current and future course of prostate cancer therapeutic development. Namely, what are the next therapeutic strategies that can hopefully be even more impactful in the decade to come? The series of articles in this special issue will discuss some of the possible strategies that can be developed in the near future.

Chemotherapy has long been a staple in the treatment for prostate cancer. When the androgen-targeted signaling agents such as abiraterone and enzalutamide first emerged, their relatively favorable toxicity profile combined with efficacy led some to speculate that chemotherapy may no longer be necessary in prostate cancer. Unfortunately, the clinical efficacy of antiandrogen therapy had its limits with meaningful but not universally dramatic extensions in survival for men with mCRPC. Furthermore, overlapping mechanisms of resistance among abiraterone and enzalutamide have been identified, suggesting that sequential efficacy of these agents may be minimal for many patients.7 Those realities combined with the relatively new-found effectiveness of chemotherapy (from just six infusions) in metastatic castration-sensitive prostate cancer have reminded clinicians about the necessary role of chemotherapy in prostate cancer.8 Dr. Nader and colleagues will review the origins and potential future strategies for chemotherapy in the treatment of prostate cancer.

To understand the unique aspects of prostate cancer, a better understanding of how to effectively target the disease within the bone microenvironment is required. Unlike most other major cancers, for reasons we still do not understand, prostate cancer metastasizes primarily to the bone in the overwhelming majority of men with prostate cancer. Until recently, this understanding has not been fully exploited therapeutically. Drs. Dorf and Agarwal will not only review data involving radiopharmaceuticals but also review the role of bisphosphonates and rank-ligand inhibition as therapeutic and supportive measures for men with prostate cancer.

For years, PSA has been the main biomarker in prostate cancer. As controversy continues to swirl around its role in screening, the search is on for biomarkers that can assist in treatment selection. ARV-7, DNA damage repair mutations, and microsatellite instability may be emerging as requisite biomarkers for all patients with advanced prostate cancer, but again the location of disease primarily in the bone may make tissue acquisition for such biomarker analysis challenging.9 7 Thus, additional approaches may be necessary; Drs. Gourdin and Sonpavde will discuss burgeoning techniques involving assessment of circulating tumor cells and circulating DNA.

Many experts ponder what will be the next therapeutic horizon in prostate cancer beyond the androgen receptor axis. Many new targets are being cultivated and have robust supporting data based on preclinical models. Dr. Erix and colleagues discuss the novel target of peroxisome proliferator-activated receptor gamma (PPARγ) and how PPARγ inhibition may represent a future therapeutic option in prostate cancer. In addition, Vitamin D and associated signaling have been extensively studied in prostate cancer preclinically and in the phase III setting as well. Dr. Trump et al. discusses that there potentially remain unexploited possibilities involving targeting of the Vitamin D pathway.

One of the primary therapeutic questions that hover menacingly over the prostate cancer therapeutic landscape is the lack of immunotherapeutic advances since the approval of sipuleucel-T in 2010. Despite the emergence of immune checkpoint inhibitors
in the years that have followed, there has been no further progress on the immunologic front in prostate cancer.\textsuperscript{10,11} That said, the future of immunotherapy remains an area of active research and ultimately, as discussed by Dr. Cordes \textit{et al.}, immunotherapeutic combinations may yield clinical benefit.

Despite the multiple questions regarding the future of the clinical management of prostate cancer, the plethora of possibilities provides reason for optimism for both patients and practitioners. This special issue highlights just some of the many potential breakthroughs that may launch the next therapeutic revolution in prostate cancer; one that not only matches what has been seen in the last decade, but hopefully surpasses it. Ultimately, the advances in the years to come will improve therapeutic opportunities for men with prostate cancer, perhaps making actual and functional cures more frequent, thereby minimizing the morbidity and mortality associated with this disease.

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