Preface

Immunotherapy for Genitourinary Cancers: New Opportunities for Clinical Impact

Sujit S. Nair, PhD

Ashutosh K. Tewari, MBBS, MCh, FRCS (Hon)

Editors

It would be an understatement to say that the concept of immunotherapy—the treatment of cancer through suppression or stimulation of the immune system—was slow to gain acceptance. A century passed between the publication of William B. Coley's report of a treatment for sarcoma employing "bacterial toxins" and the first Food and Drug Administration–approved immunotherapy in 1990, bacillus Calmette-Guérin (BCG) for bladder cancer. In the 30 years since, immunotherapy has revolutionized cancer treatment. Today, there are nearly 3 dozen approved immunotherapeutics for 20 different cancers, and despite ongoing challenges, advances in research have resulted in remarkable impact on clinical practice.

Immunotherapy in genitourinary (GU) cancers presents significant opportunities, especially in the context of recent breakthroughs. As the articles in this issue of *Urologic Clinics* describe, approvals of immune checkpoint blockade have changed the standard of care for advanced renal carcinomas, with a number of these strategies now approved as first- and second-line treatments. A growing body of evidence suggests that in biochemically recurrent prostate cancer, for which there is currently no current standard of care or systemic therapy, immune-based therapies may slow disease progression. Despite the persistent challenges prostate cancer creates for immunotherapy drug development, pivotal clinical trials have pointed to potential combinations of therapies that may be effective, and new studies have highlighted the emerging role of immunotherapy for localized prostate cancer. Novel combinations of immunotherapies have also shown promise in both early- and late-stage bladder cancers, particularly in patients who have not responded well to BCG.

The articles in this issue highlight breakthroughs, as well, in our understanding of the biology of urologic tumors. Recent studies have shown that natural killer (NK) cells infiltrate urologic tumors and that these cells are often dysfunctional. Preclinical data and research in human cells have demonstrated the potential of immunotherapeutic interventions to alleviate this dysfunction, and diverse NK-cell-centric clinical trials are underway in bladder, kidney, and prostate cancers. In addition, in prostate cancer specifically, other next-gen immunotherapy approaches that exploit the prostate-specific lineage surface protein targets are a compelling and growing new area: bispecific T-cell engagers, antibody-drug conjugate therapy, and third-generation chimeric antigen receptor T cells.

Development of targeted cell and gene therapies will benefit greatly from the advent of single-cell sequencing, which will help address one of the most challenging aspects of understanding

Urol Clin N Am 47 (2020) xi–xii
https://doi.org/10.1016/j.ucl.2020.08.001

and treating cancer—heterogeneity. Single-cell sequencing technologies make it possible to characterize the key contributions to the disease of specific cell subpopulations in both the tumor and the tumor microenvironment (TME), including a network of noncancerous cells types and extracellular matrix proteins outside of the tumor that may contribute to disease progression. The complexity of the TME has only recently been appreciated but will be extremely important moving forward, especially in delineating the distinctions between urologic cancers. Given their immunologically distinct TME, better understanding of the TME in bladder and prostate cancers will be critical for successful development of intratumoral neoadjuvant immunotherapy approaches that target early cancer clones before they have modified the tumor environment.

Identification of subpopulations of cells in the TME will enable identification of new therapeutic targets and disease biomarkers and ultimately enable better understanding of why some patients respond to a particular therapy while others do not. Understanding differentiated response to treatment has, arguably, been one of the most complex and perplexing aspects of immunotherapy. While such immunotherapies as checkpoint blockade have resulted in a paradigm shift in disease management, the fact remains, nonetheless, that cancer is not cured in the majority of patients, and both academic and industry investigators are sharply focused on discovery and testing of novel combinations of therapies.

As described in this issue, immuontherapy in metastatic settings remains especially challenging. Genomic approaches will enable better understanding of "lethal" phenotypes, specifically in the case of prostate cancer, and of metastatic disease across GU cancers, and will support discovery of novel biomarkers for the development of targeted approaches. Preclinical animal models may be especially useful for advancing such strategies. Finally, much work continues to develop a more nuanced understanding of the intricacies of the innate immune system in the context of GU cancers, specifically, the mechanisms that play a role in the activation of immunity or in immune escape.

These review articles demonstrate the need for, and potential of, targeted and customized approaches, cancer by cancer, and patient by patient. They demonstrate the promise of novel combinatorial strategies in the context of better understanding of the complex biology of GU cancers and the advent of innovative tools for analysis and prediction. We hope this special issue, with 13 articles, including 4 online-only articles, has conveyed the realistic and not insubstantial challenges and significant opportunities for GU cancer immunotherapy.

Sujit S. Nair, PhD
Department of Urology
Icahn School of Medicine at Mount Sinai
Annenberg 24-15
New York, NY 10029, USA

Ashutosh K. Tewari, MBBS, MCh, FRCS (Hon)
Department of Urology
Icahn School of Medicine at Mount Sinai
Mount Sinai Health System
One Gustave L. Levy Place
Box 1272 L6-57
New York, NY 10029, USA

E-mail addresses:
Sujit.nair@mountsinai.org (S.S. Nair)
Ash.tewari@mountsinai.org (A.K. Tewari)