About the Editor

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Ronald Bukowski is an emeritus staff at the Cleveland Clinic Foundation, and Professor of Medicine, Cleveland Clinic Lerner College of Medicine, Case Western Reserve University (OH, USA). He was recently the Deputy Director of the Cleveland Clinic Taussig Cancer Center and Director of the Experimental Therapeutics at the Cleveland Clinic Cancer Center. He held the James Zito Chair in Cancer Research at the Taussig Cancer Center from 2001 to 2008, and in 2008 retired from active practice. He is a fellow of the American College of Physicians and member of numerous professional societies, including the American Society of Clinical Oncology and the American Society of Hematology. He is a lifelong researcher with interests in biologic response modifiers, the biology of renal cell carcinoma, and new drug development and investigation.

Foreword

Targeted therapy for renal cell carcinoma

Ronald M Bukowski

Renal cell carcinoma (RCC) accounts for approximately 3% of malignancies, and is the seventh leading cause of death in the USA. An estimated 58,000 new renal tumors were diagnosed in 2010, with 13,000 deaths recorded [1]. Globally, it is estimated that over 200,000 new cases are diagnosed each year [101]. This neoplasm is the most common in the seventh decade of life, and a consistent finding is a male predominance (2:1). Notably, there has been significant progress in the understanding and management of this tumor within the past 10 years, and the emerging surgical and systemic therapy strategies have revolutionized its management. The focus of this book is therapy for patients with metastatic RCC (mRCC), specifically, the new treatment paradigm that has recently emerged.

Current approaches for mRCC patient management utilize a knowledge of histology, molecular abnormalities, clinical prognostic factors and the efficacy/toxicity of available treatments. Prior to 2006, immunotherapy was the standard of care, but its effects remain controversial. Development of therapies that target relevant biologic pathways has evolved. Agents blocking angiogenic pathways, including sunitinib, pazopanib, sorafenib, bevacizumab, everolimus and temsirolimus, have demonstrated efficacy and offer new strategic options for the patients with mRCC. The 11 chapters in this book review and summarize the current status of this therapy.

The authors have addressed a variety of relevant management issues, with the initial chapter by Bernard Escudier reviewing various biologic pathways

in RCC. The VEGF and mTOR pathways are the primary focus, specifically, how their inhibition affects tumor progression. This chapter provides an excellent overview of the biologic mechanisms operative, and sets the stage for the next four chapters.

The traditional approach utilized in managing mRCC patients involved administration of cytokines, such as IL-2 or IFN- α . This has since been replaced by administration of various targeted agents, including mTOR inhibitors, tyrosine kinase inhibitors and VEGF antibodies. Chapter 2 provides an overview of the PI3K/Akt/mTOR signaling cascade and its regulation of the HIF nuclear transcription factors. The development of mTOR inhibitors and the clinical activity of temsirolimus and everolimus are described. Chapters 3 and 4 review the new treatment paradigm for advanced RCC utilizing inhibition of the VEGF pathway and Chapter 5 provides an overview of the future potential of targeted immunotherapy with a focus on anti-CTLA-4 and PD-1 monoclonal antibodies.

The next group of chapters (6–10) provide the reader a summary of previous clinical investigations in RCC utilizing EGFR inhibitors, cytokines, chemotherapy, bisphosphonates and vaccines. In Chapter 9, previous vaccine trials in RCC are reviewed, and their future potential is explored. The possibility of improving the activity of various peptide and cell-based approaches by utilizing coadministration of agents such as sunitinib or ipilumimab (anti-CTLA-4 monoclonal antibody) is of interest.

Chapter 11 reviews future approaches for the treatment of mRCC, such as the novel agents axitinib and tivozanib, two third-generation VEGFR tyrosine kinase inhibitors, and the potential of combination therapy with the approved tyrosine kinase inhibitors and mTOR inhibitors. The authors note that the available data suggest these combinations have either excessive toxicity or activity comparable with single agents. Combinations that involve drugs with different mechanisms of action or different modalities, such as VEGF-targeted therapy, and the new group of targeted immunotherapeutic agents are strategies to be investigated.

In summary, the authors have provided a comprehensive yet succinct review of therapy for advanced RCC. The clinical advances within a short timespan have been amazing, and currently, consolidation of the clinical findings, investigation of the mechanisms underlying the activity of the various targeted agents and the resistance that develops in most instances are needed. Since the therapeutic results to date provide disease control for a limited time, investigations of novel approaches are still needed. Revisiting the role of immunotherapy may be an important component of future therapeutic advances, and importantly,

identification of new targets and relevant pathways in RCC, such as PBRM1 [2], will provide potential clues for development of new therapeutic strategies.

Financial & competing interests disclosure

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