frontiers in ONCOLOGY

SPECIALTY GRAND CHALLENGE ARTICLE
published: 10 October 2011
doi: 10.3389/fonc.2011.00032

Genitourinary oncology: current status and future challenges

Ronald M. Bukowski*

Cleveland Clinic Foundation, Cleveland Clinic Taussig Cancer Center, Pepper Pike, OH, USA
**Correspondence: bukow464@sbcglobal.net*

INTRODUCTION

Genitourinary oncology (GU Oncology) focuses on research and treatment of urinary system cancers in both genders, as well as malignancies affecting the male sexual organs. Sites included are the kidneys, bladder, prostate, and testes. These malignancies represent approximately one fourth of all solid tumors, however, the field remains underrepresented in the basic science, epidemiologic, clinical research, and translational research literature. The Genitourinary Oncology Section of Frontiers in Oncology is a welcomed addition to the medical literature, and will provide an important mechanism for publication of reviews and research in this field. The purpose of this manuscript is to briefly review the field, and outline some of the challenges confronting GU Oncology clinical and basic researchers.

Since the 1970s, the advantages of a multimodality approach in GU tumors has been recognized, and many of the advances represent the combined efforts of urologists, medical, and radiation oncologists, as well as basic research scientists. Among the early reports in this era was the development of curative therapy for advanced nonseminomatous testicular cancer utilizing platinum based chemotherapy and surgical resection of residual disease (Hayes-Lattin and Nichols, 2009). Utilizing the treatment paradigm of combined modality therapy, therapeutic advances in renal cell, bladder, and prostate cancers (PC) have subsequently occurred.

PROSTATE CANCER

Prostate cancer is the most common noncutaneous cancer in men and accounted for an estimated 217,000 new cases annually the USA in 2010 (Jemel et al., 2010). PC develops initially as an androgen dependent disease that relies on the androgen receptor (AR) for growth and progression (Wilson, 2010), but then develops into a castration-resistant PC (CRPC) during androgen deprivation therapy (Antonarakis and Eisenberger, 2011). Understanding the molecular and genetic events occurring during progression and responsible for the acquisition of the castrate-resistant phenotype is needed. Clinically, significant progress in diagnosis and management of PC has been made, however, numerous issues remain controversial including screening, chemoprevention, active surveillance, and therapeutic approaches to localized disease. New treatment options for CRPC include the tumor vaccine Sipuleucel-T (Kantoff et al., 2010), various chemotherapy options, and novel agents such as the CYP17 inhibitor abiraterone acetate (administered with prednisone; de Bono et al., 2011). Patient outcomes have improved, but the durations of progression-free and overall survival still remains relatively short and further improvement is needed. Areas such as the biology and treatment of bone disease and metastases should be active areas of investigation. Finally, validated clinical, radiologic, biologic, and genomic response biomarkers are needed, which may then act as surrogates of clinical benefit.

RENAL CELL CARCINOMA

Renal cell carcinoma (RCC) accounts for approximately 3% of all malignancies, and was formerly only treatable by surgery. Over the past 10 years there has been significant progress in the understanding and management of this tumor, with new surgical and systemic therapy strategies revolutionizing its management. A recent major advance in RCC is the realization that this disease is not a single entity but rather a collection of different tumor types, each derived from the various parts of the nephron and possessing distinct genetic characteristics, histologic features, and to some extent clinical phenotype. Clear cell carcinoma, the most common histologic subtype, has been extensively studied, and investigations into the molecular, biologic, and clinical aspects of the non-clear cell subtypes are now needed.

A major advance in understanding RCC was the recognition that the Von Hippel–Lindau (VHL) factor, a negative regulator of hypoxia-inducible factor (HIF), is encoded by a tumor suppressor gene which lost in >75% of clear cell RCCs (Kaelin, 2007). Inactivation of VHL results in increased HIF availability in tumor cells and subsequent transcriptional upregulation of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and a variety of other targets (Kaelin, 2007). Activation of the mammalian target of rapamycin (mTOR) pathway also leads to increases in HIF production (Thomas et al., 2006). The VEGF and the mTOR pathways have been targeted for drug development and therapeutic approaches have focused on these targets. Current approaches for management of metastatic RCC (mRCC) utilize 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. Agents blocking angiogenic pathways, including sunitinib, pazopanib, sorafenib, bevacizumab, everolimus, and temsirolimus, have demonstrated efficacy in mRCC (Brian, 2010). Investigations of additional genetic abnormalities (PBRM1, SETD2, UTX), mechanisms of resistance, and development of novel agents (axitinib, tivozanib) area priority. Additionally, the roles of immune therapy and immunoregulation in mRCC are again under study. Immune checkpoint inhibitors such as monoclonal antibodies recognizing CTLA-4 and PD-1 are in clinical trials, and the effects on tumor associated immunosuppression and immunoregulation of therapeutic agents are being evaluated. Vaccine development strategies and clinical trials are again considerations.

Surgical developments during the last 10–15 years include defining the role of minimally invasive surgery, active surveillance for small (<4.0 cm) masses, and nonsurgical ablative techniques (cryoablation, radiofrequency ablation). Tumor staging and clinical features identify a population of RCC patients at high risk of recurrence after

surgery. The TKI's sunitinib, sorafenib, and pazopanib are being studies as postoperative adjuvant therapy. Additionally, identification of biomarkers in high risk patients, and utilization gene expression patterns to define risk groups are under study.

BLADDER CANCER

Bladder cancer remains a common malignancy in Western society, with global incidence of over 356,000 new cases per year (Ploeg et al., 2009). Most tumors are transitional cell carcinomas (TCC). Diagnostic cystoscopy remains the gold standard for detecting lower urinary tract malignancies. Urine cytology remains the most specific adjunct to cystoscopy for detection and surveillance of bladder tumors (Sexton et al., 2010). Many biomarkers have been utilized for the diagnosis, surveillance, and management of bladder cancer (Parker and Speiss, 2011), however, the ideal marker has not yet been identified.

At diagnosis, >70% of bladder tumors will be non-muscle–invasive (stage Ta/T1) tumors, with the rest being muscle–invasive (stages T2-4). In non-muscle–invasive tumors, recurrence and progression to muscle–invasive disease are the critical steps that dictate therapy and are associated with worse survival rates. Additional biological and molecular insights into the pathogenesis of muscle–invasive bladder cancer are needed to permit adequate and appropriate therapy and decrease the progression rates. The genetic and epigenetic changes responsible for tumor development, and the molecular pathways associated with these alterations should be a focus of investigation. An example is the recent report of whole-exome sequencing (Gui et al., 2011) of genomic DNA from TCC.

Radical cystectomy accompanied by pelvic lymph node dissection (PLND) remains the standard surgical treatment for muscle–invasive bladder cancer. The roles of postoperative adjuvant chemotherapy and preoperative neoadjuvant chemotherapy have been evaluated. The available evidence therefore supports the integration of neoadjuvant chemotherapy with cystectomy for muscle–invasive bladder cancer, but this approach has yet to receive wide acceptance (Bajorin and Herr, 2011). Further understanding the biology, molecular aspects, and metastatic potential of bladder cancer may permit tailoring therapy for the highest risk patients.

In patients with advanced and metastatic disease, combination chemotherapy with cisplatin-based combination chemotherapy is associated with improved outcomes, but most patients relapse and die of progressive disease (Ismalli et al., 2011). Current regimens produce suboptimal outcomes in the frontline setting with no proven effective second-line regimen. Patients with metastatic TCC in both the frontline and salvage chemotherapy settings should be considered candidates for clinical trials utilizing novel agents.

SUMMARY

Significant advances in therapeutic approaches to the various GU malignancies have occurred over the past 10–15 years. Tools such as genomic analysis, various molecular biologic techniques, and biochemistry, are providing additional insights. Personalized approaches to GU tumors are not yet a reality, but certainly are a likely outcome of current research.

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Received: 16 September 2011; accepted: 20 September 2011; published online: 10 October 2011.

*Citation: Bukowski RM (2011) Genitourinary oncology: current status and future challenges. Front. Oncol. **1**:32. doi: 10.3389/fonc.2011.00032*

This article was submitted to Genitourinary Oncology, a specialty of Frontiers in Oncology.