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Recent advances in genitourinary tumors: A review focused on biology and systemic treatment

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ABSTRACT

Updated information published up to 2016 regarding major advances in renal cancer, bladder cancer, and prostate cancer is here presented. Based on an ever better understanding of the genetic and molecular alterations that govern the initial pathogenic mechanisms of tumor oncogenesis, an improvement in the characterization and treatment of urologic tumors has been achieved in the past year. According to the Cancer Genome Atlas (ATLAS) project, alterations in the *MET* pathway are characteristics of type 1 papillary renal cell carcinomas, and activation of *NRF2-ARE* pathway is associated with the biologically distinct type 2. While sunitinib and pazopanib continue to be the standard first-line treatment in metastatic renal cell carcinoma of clear cell histology, nivolumab and cabozantinib are now the agents of choice in the second-line setting. In relation to urothelial bladder carcinoma, new potential molecular targets such as *FGFR3*, *PI3 K/AKT*, *RTK/RAS*, *CDKN2A*, *ARIDIA*, *ERBB2* have been identified. Response to adjuvant cisplatin-based chemotherapy appears to be related to basal, luminal, and p53-like intrinsic subtypes. A phase II study with eribulin and a maintenance phase II trial with vinflunine have shown promising results. Similarly, the use of the check point inhibitors in advanced disease is likely to revolutionize the management of patients who have progressed after cisplatin-based chemotherapy. In prostate cancer, seven mutually exclusive molecular subtypes have been identified by the TCGA project. Chemotherapy has been consolidated as a key treatment for castration-sensitive metastatic prostate cancer, and abiraterone, enzalutamide, cabazitaxel, and radium-223 remain standard therapeutic options for men with metastatic castration-resistant prostate cancer. All this progress will undoubtedly contribute to the development of new treatments and therapeutic strategies that will improve the survival and quality of life of our patients.

1. Introduction

Genitourinary cancers, in particular carcinoma of the kidneys, bladder, and prostate take a large toll on human health and placed significant economic burden on health care systems. Prostate cancer ranks as the leading genitourinary cancer in the US, followed by bladder and kidney cancer, is the second most frequently diagnosed cancer and the sixth leading cause of cancer death among American males (Jemal et al., 2011). Renal cell carcinoma (RCC) accounts for approximately 2% of all types of cancers, which is growing annually at 1.5–5.9% around the world (Key statistics, 2017). Bladder cancer is the ninth most common cancer in the world, with an estimated of 430,000 new cases diagnosed in 2012 (Torre et al., 2015). A better understanding of the biology of urologic malignancies has led to a rapid change in their therapeutic landscape. With the approval of several novel agents in each of these tumors, understanding appropriate patient selection, mechanisms of resistance and optimal treatment sequence are critical components to improve patient outcome. Similarly, biomarker development is now a critical need in the field.

Major developments in biomolecular research, treatment strategies, and future perspectives in renal, bladder, prostate, and testicular cancer as well as milestones achieved in the last year are summarized in the present review, although some information has been reported in 2016.

2. The best in renal cancer

2.1. Molecular research

2.1.1. Molecular classifications

Kidney cancer or RCC is not a single disease but is made up of various types of cancer that are characterized by different genetic drivers; each type has distinct histologic features and different clinical course and responses to treatment. Recently, investigators of the Cancer Genome Atlas Research Network have performed an integrative genomic analysis of 161 papillary RCC (PRCC) tumors and provided molecular insights into tumor classification (The Cancer Genome Atlas Research Network, 2016). PRCC accounts for 15% to 20% of kidney cancer cases diagnosed annually. It has long been classified histologically as either type 1 or type 2, but until now much of what scientists knew about the underlying genetics of PRCC has been based on information garnered from rare, inherited forms of the disease. Little was known about the molecular background of cases that occur without a family history of kidney cancer. Currently, there are no effective therapies for advanced PRCC. In the study of the Cancer Genome Atlas Research Network, a cross platform analysis was performed of 161 papillary renal tumors, including 75 type 1 (predominantly stage I), 60 type 2 (frequently stage III or IV), and 26 that could not be classified as type 1 or 2. The study involved careful pathologic review by multiple genitourinary pathologists and a comprehensive series of analysis, including whole-exome sequencing, copy-number analysis, messenger RNA and microRNA sequencing, DNA-methylation analysis, and proteomic analysis. Single-nucleotide-polymorphism array studies identified three main tumor subgroups: one subgroup, composed predominantly of type 1 was defined by multiple chromosomal gains (chromosomes 7 and 17) and the other two subgroups were predominantly type 2 tumors, one of these had few copy-number alterations, and the other had multiple chromosomal losses, including frequent loss of chromosome 9p. Also, whole-exome sequencing identified 10,380 putative somatic mutations in 157 tumors with an average of 1.45 nonsilent mutations per megabase, Five genes (*MET, SETD2, NF2, KDM6A*, and *SMARCB1*) that