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European Association of Urology

Platinum Priority – Collaborative Review – From Lab to Clinic

Editorial by XXX on pp. x–y of this issue

The Emergence of Precision Urologic Oncology: A Collaborative Review on Biomarker-driven Therapeutics

Christopher E. Barbieri [a,b,*], *Arul M. Chinnaiyan* [c], *Seth P. Lerner* [d], *Charles Swanton* [e], *Mark A. Rubin* [a,b,f]

[a] *Department of Urology, Weill Cornell Medical College, New York, NY, USA;* [b] *Sandra and Edward Meyer Cancer Center of Weill Cornell Medical College, New York, NY, USA;* [c] *Michigan Center for Translational Pathology, Departments of Pathology and Urology, and Howard Hughes Medical Institute, University of Michigan Medical School, Ann Arbor, MI, USA;* [d] *Scott Department of Urology, Baylor College of Medicine, Houston, TX, USA;* [e] *University College London Cancer Institute, Cancer Research UK Lung Cancer Centre of Excellence, London, UK;* [f] *Englander Institute for Precision Medicine, Weill Cornell Medical College, New York, NY, USA*

Article info

Article history:
Accepted August 9, 2016

Associate Editor:
Stephen Boorjian

Keywords:
Precision Medicine
Mutations
Sequencing
Genomics

Abstract

Context: Biomarker-driven cancer therapy, also referred to as precision oncology, has received increasing attention for its promise of improving patient outcomes by defining subsets of patients more likely to respond to various therapies.
Objective: In this collaborative review article, we examine recent literature regarding biomarker-driven therapeutics in urologic oncology, to better define the state of the field, explore the current evidence supporting utility of this approach, and gauge potential for the future.
Evidence acquisition: We reviewed relevant literature, with a particular focus on recent studies about targeted therapy, predictors of response, and biomarker development.
Evidence synthesis: The recent advances in molecular profiling have led to a rapid expansion of potential biomarkers and predictive information for patients with urologic malignancies. Across disease states, distinct molecular subtypes of cancers have been identified, with the potential to inform choices of management strategy. Biomarkers predicting response to standard therapies (such as platinum-based chemotherapy) are emerging. In several malignancies (particularly renal cell carcinoma and castration-resistant prostate cancer), targeted therapy against commonly altered signaling pathways has emerged as standard of care. Finally, targeted therapy against alterations present in rare patients (less than 2%) across diseases has the potential to drastically alter patterns of care and choices of therapeutic options.
Conclusions: Precision medicine has the highest potential to impact the care of patients. Prospective studies in the setting of clinical trials and standard of care therapy will help define reliable predictive biomarkers and new therapeutic targets leading to real improvement in patient outcomes.
Patient summary: Precision oncology uses molecular information (DNA and RNA) from the individual and the tumor to match the right patient with the right treatment. Tremendous strides have been made in defining the molecular underpinnings of urologic malignancies and understanding how these predict response to treatment—this represents the future of urologic oncology.

* Corresponding author. Weill Medical College of Cornell University, Urology, 525 East 68th Street, Starr 900, New York, NY 10065, USA. Tel. +12127465562; Fax: +1212 746 0975.
E-mail address: chb9074@med.cornell.edu (C.E. Barbieri).

http://dx.doi.org/10.1016/j.eururo.2016.08.024

1. Introduction

The past decade has seen an explosion of therapeutic options in urologic oncology, across multiple cancer types. Renal cell carcinoma (RCC) patients now have options of tyrosine kinase inhibitors, mechanistic target of rapamycin (mTOR) inhibitors, and immunotherapy agents. The prostate cancer field has seen the approval of over half a dozen novel agents in the past few years, as well as shifting paradigms regarding the temporal sequencing of agents [1,2]. Urothelial carcinoma, in addition to defining subsets of patients with best response to standard of care chemotherapeutic options, appears poised for novel agents to make meaningful impact as well. Clearly, this is an exciting time to be in urologic oncology, as there is more promise and hope for our patients than ever before.

Each novel therapy improves outcomes compared with previous generations of standard therapy, but unfortunately, the recent improvements in patient survival can be described as incremental rather than transformative. However, defined subsets of patients respond well to each therapy, and it is likely that these subsets of responders are not the same for all different therapeutic options. The example of trastuzumab (Herceptin) in breast cancer treatment may serve as a model for successful development of precision medicine approaches. Trastuzumab was the first rationally designed targeted therapy for solid tumors, based on the discovery that some breast cancers have a high degree of amplification of *Her2/neu* [3], and that these cancers are associated with worse prognosis [4]. Development of the drug from bench to approval spanned 13 yr—and it has now been responsible for a dramatic change in outcome for women for this subtype of breast cancer.

In urologic oncology, now comes the challenge of taking these diverse therapeutic opportunities, and finding ways to match the right therapy with the right patient: the paradigm of precision medicine. In this review we will explore the history, challenges, and opportunities inherent in this process, and explore the future of biomarker-driven therapeutics in urologic oncology (Fig. 1).

Biomarker-driven therapy can refer to multiple approaches to patient stratification and selection of management strategies. First, this can refer to classic targeted therapy, in which a specific gene product serves as both the biomarker and the target of therapeutic action—*HER2* overexpression in breast cancer, or *BRAF* mutations in melanoma, are classic examples [5]. Secondly, biomarkers may distinguish patients that are preferentially sensitive (or resistant) to standard therapeutic options, even though these specific biomarkers are not targets themselves (such as triple negative breast cancer or *KRAS* mutated colorectal cancers). Finally, distinct subclasses of cancers may respond in fundamentally different manners to various therapeutic interventions—many such subclasses may be identifiable using histologic criteria, but others may only be exposed using specific molecular biomarkers. We will review these concepts across urologic oncology in a relatively disease-specific manner. In addition, we will also discuss issues that apply more universally, across multiple malignancies and multiple signaling pathways. These include concepts of utilizing biomarker-driven stratification to determine sequencing of different therapeutic options, implications of tumor heterogeneity for biomarker-driven

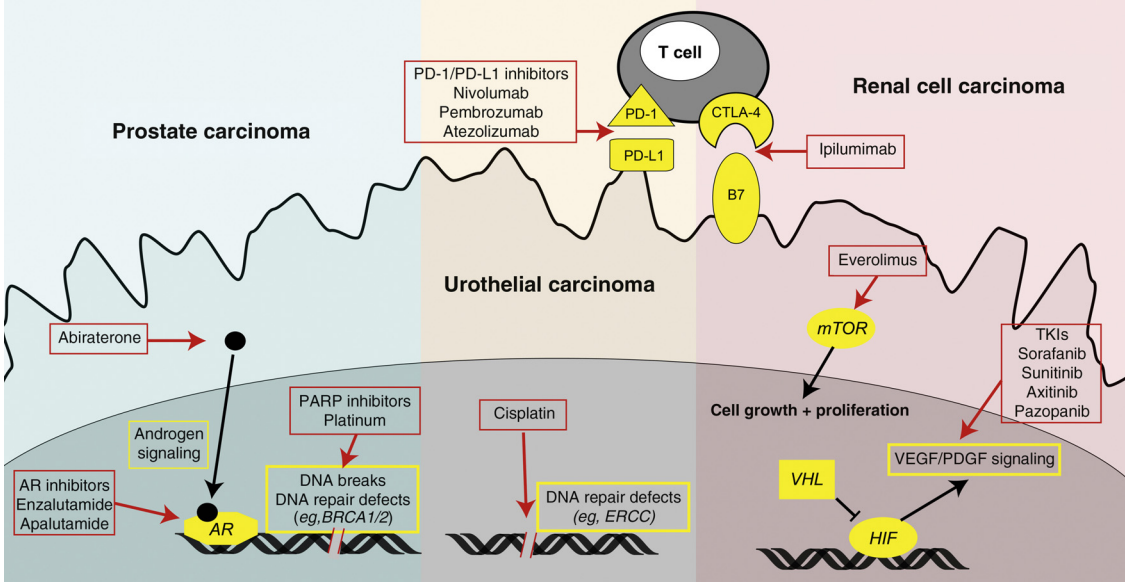

Fig. 1 – Landscape of precision urologic oncology. Relevant biological pathways, therapeutic targets, and therapies are highlighted for prostate cancer (left), urothelial cancer (center), and renal cell carcinoma (right). Therapeutics are outlined in red; biological pathways and targets are shown in yellow. Immunotherapy approaches using checkpoint inhibitors (top) may be applicable across disease histologies, with the most current evidence in renal and urothelial cancer.
AR = androgen receptor; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; mTOR = mechanistic target of rapamycin; PD-1 = programmed cell death protein 1; PDGF = platelet-derived growth factor; PD-L1 = programmed death-ligand 1; TKIs = tyrosine kinase inhibitors; VEGF = vascular endothelial growth factor.

Please cite this article in press as: Barbieri CE, et al. The Emergence of Precision Urologic Oncology: A Collaborative Review on Biomarker-driven Therapeutics. Eur Urol (2016), http://dx.doi.org/10.1016/j.eururo.2016.08.024