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Review

The New Age of *-omics* in Urothelial Cancer – Re-wording Its Diagnosis and Treatment

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ABSTRACT

Unmet needs in urothelial cancer management represent an important challenge in our effort to improve long-term overall and disease-free survival rates with no significant compromise in quality of life. Radical cystectomy with pelvic lymph node dissection is the standard for the management of muscle-invasive, non-metastatic cancers. In spite of a 90% local disease control, up to 50% of patients ultimately die of distant metastasis. Bladder preservation using chemo-radiation is an acceptable alternative, but optimal patient selection remains elusive. Recent research is focused on the employment of tailored-made strategies in urothelial cancer exploiting the potential of theranostics in patient selection for specific therapies. Herein, we review the current knowledge on molecular theranostics in urothelial cancer and we suggest that this is the time to move toward imaging theranostics, if tailored-made disease management and patient stratification is envisaged.

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1. Introduction

Historically, the inception of theranostics dates from 1940, when radioactive iodine was employed for the imaging and management of thyroid cancers. In 1998, John Funkhouser coined the term "theranostics" in

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a press release during which he described a material which allowed jointly disease diagnosis, treatment and monitoring (Kelkar and Reineke, 2011). Since then, the advances in molecular understanding of disease mechanisms and molecular imaging have been fostering theranostics that now integrates molecular targeting vectors and nanoplatform technologies for diagnosis and therapy (Nicolaides et al., 2014). As such, it could be argued that theranostics facilitates predictive, preventive, personalized and participatory medicine (Bradley et al., 2011), with obvious advantages in cost-effectiveness and quality of clinical care. Such aspects are pertinent to complex disease and/or clinical phenotypes, such as cancer.

Urothelial cancer is the sixth most common cancer in the USA with an estimation of 16,000 deaths and 74,000 new cases per year (Howlader et al., 2016). In Europe, approximately 151,297 new cases of urothelial cancer were diagnosed in 2012, with an age-standardized incidence rate (per 100,000 persons) of 3.5 for females and 17.7 for males. The annual crude incidence rate is 20.4/100000, while in 2012, the annual crude mortality rate was 7.1/100,000. Most cases present with non-invasive disease, but about one third of these patients will progress to muscle-invasive disease, while 30% exhibit muscle invasion with or without metastases upon diagnosis (Howlader et al., 2016; Bamias et al., 2016). Radical cystectomy (RC) with pelvic lymph node dissection (LND) is the treatment of choice (Bellmunt et al., 2014). Cisplatin-based chemotherapy is the cornerstone of systemic therapy for urothelial cancer (Bamias et al., 2013). Neoadjuvant chemotherapy has long been a standard for muscle-invasive urothelial cancer, although it is very underutilized (Galsky et al., 2015). For patients who do not undergo neoadjuvant chemotherapy, adjuvant chemotherapy may be considered in cases of high-risk for relapse after RC (Galsky et al., 2011). Radiosensitizing systemic chemotherapy is also a critical component of bladder- preserving approaches where radiotherapy is the main treatment modality (Krengli et al., 2017). Finally, cisplatin-based combination chemotherapy has been the treatment of choice in inoperable or metastatic disease, with long-term survival reported in about 20% of patients (Necchi et al., 2017).

In spite of considerable improvements in outcomes during the last 40 years, there are still important unmet needs in urothelial cancer management, both in terms of efficacy and cure, but also in issues affecting the quality of life, especially in therapies for localized disease. For example, RC radical cystectomy, needs urinary diversion (Dellis et al., 2014) and may cause erectile impotence and infertility, whereas widely accepted criteria for optimal patient selection for bladder preservation strategies are still lacking. The advent of modern immunotherapy, which inhibits the interaction between the programmed-death 1 (PD-1) receptor on T-lymphocytes involved in tumor immunesurveillance and its ligand PD-ligand 1 (PD-L1) has created promising therapies for bladder cancer (Bellmunt et al., 2017). The emergence of targeted therapies has renewed the interest in individualizing treatment in urothelial cancer by identifying biologically relevant molecular factors, which could aim patients' selection for specific agents.

An extensive list of key molecules, implicated in cell proliferation and apoptosis, cell cycle regulation, cell adhesion, hypoxia, and angiogenesis may serve as candidate predictive and/or prognostic biomarkers in urothelial cancer (Aoun et al., 2015). Furthermore, recent advances in tumor genome analysis have revolutionized our understanding of tumors' distinct biology and will probably lead to a molecularly-driven subtyping of this disease (Damrauer et al., 2014). Herein, we aim to (i) review the current knowledge on molecular theranostics in urothelial cancer, following up on pharmacogenomics, metabolomics, proteomics and/or peptidomics data, (ii) analyze in detail those findings related to the most studied of them as well as their current clinical applications and (iii) exploit this information to design new or better diagnostic and therapeutic strategies for urothelial cancer especially in the era of precision medicine.

2. Precision Medicine in Urothelial Cancer

The last decade witnessed an intense effort toward precision medicine of human malignant neoplasms. This trend has been recently followed in urothelial cancer, too. Only in 2015, 747 clinical studies (Massari et al., 2015) investigated the possible role of omics and multi-omics strategies, such as pharmacogenomics (Katsila and Patrinos, 2015), metabolomics (Zhou et al., 2017), proteomics or peptidomics (Di Meo et al., 2016) in personalizing treatment in urothelial cancer. In such a big data era, in which the issue of single data interpretation arises, theranostics is anticipated to expedite cost-effective tailored-made disease management and patient stratification in urothelial cancer. Several molecules have been studied so far for their potential in contributing to precision medicine in urothelial cancer patients (Table 1). We are analyzing in detail the data related to the most studied of them as well as their current clinical applications.

2.1. Vascular Endothelial Growth Factor (VEGF)

Even though preclinical findings have indicated that the VEGF axis is important in urothelial carcinoma (reviewed in Ghosh et al., 2014), there has been little clinical investigation of vascular inhibition in urothelial cancer patients (Grivas et al., 2014). The use of tyrosine kinase (TKI) inhibitors of the VEGF receptor has not been associated with considerable efficacy in relapsed bladder cancer, although occasional responses have been reported. In 2011, the Hoosier Oncology Group published a single-arm, phase II study of a 21-day cisplatin-gemcitabine regimen (including bevacizumab) in patients with advanced urothelial carcinoma (Hahn et al., 2011) and reported an overall radiographic response rate of 72% (19% were complete responses), with a median overall survival of 19.1 months. Such findings are promising, as overall survival has been in the range of 14 to 18 months with chemotherapy only in historical series (Flaig and Theodorescu, 2012). Based on this data, the Cancer and Leukemia Group B is now sponsoring a randomized, phase III study of this regimen in patients suffering from advanced urothelial carcinoma (Clinical trials. Gov identifier: NCT00942331). In the second line setting, chemotherapy plus Ramucirumab (vascular endothelial growth factor receptor 2 antibody) versus chemotherapy alone is also investigated in a Phase III trial. Chemotherapy plus Ramucirumab showed positive results in a Phase II study (Petrylak et al., 2016). The prognostic significance of the VEGF axis in urothelial cancer has been well supported, in particular when VEGFA is considered, as the latter has been identified as a major independent prognostic marker following a large-scale real-time reverse transcription-PCR strategy (Pignot et al., 2009). Several molecular pathways have been studied toward the understanding of disease mechanisms in urothelial cancer and there has been significant datasets implicating angiogenesis as a key pathway that may serve theranostics and optimum patient stratification (reviewed in Narayanan and Srinivas, 2017).

2.2. ET-1

Endothelin-1 (ET-1) and its receptor play a key role in lung metastasis in patients with urothelial cancer, which seems to depend on lung macrophage activity. At the same time, the expression levels of ET-1 correlate positively with muscle invasion in urothelial cancer. A negative correlation of ET-1 expression levels with disease-specific survival has been reported (Said et al., 2011). Findings reporting the pharmacologic inhibition of the ET-1 axis and the prevention of metastases to the lung, having a minor impact on the established primary or metastatic tumors, suggest that ET-1 receptor inhibitors will be most effective in the adjuvant therapy (Flaig and Theodorescu, 2012). Thus, ET-1 receptor inhibitors look promising for urothelial cancer, considering their availability and tolerability. Furthermore, molecular alterations of the endothelin axis have been determined in invasive urothelial cancer and compared to other prognostic markers, such as kinase inhibitor 67

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