Urinary Bladder Cancer

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Urinary bladder cancer (UBC) is the most common malignancy of the urinary tract in humans, with an estimated global prevalence of 1.1 million cases over 5 years. Because of its high rates of recurrence and resistance to chemotherapy, UBC is one of the most expensive cancers to treat, resulting in significant health care costs.

Keywords: bladder cancer ; organoids ; exosomes ; precision medicine ; one health

1. Introduction

Urinary bladder cancer (UBC) is a common urogenital malignancy causing approximately 80,000 new cases and 18,000 deaths each year in the United States alone [1][2]. Urothelial carcinoma accounts for 90% of bladder cancers and can be categorized into non-muscle invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC) subtypes; although the majority of UBC present as NMIBC, the MIBC subtype is associated with the highest risk of developing metastases. Overall, 75% of patients diagnosed with high-risk bladder cancer will experience tumor recurrence, advancement of cancer, or decease within 10 years of their diagnosis [1]. Transurethral resection (TUR) of all visible lesions is a standard treatment for NMIBC but is associated with a high recurrence rate [3]. Intravesical chemotherapy and immunotherapy have demonstrated significant benefit in delaying disease recurrence in patients with NMIBC [4]. In MIBC patients, neoadjuvant chemotherapy with platinum-based drugs has been offered prior to local definitive treatment and has been associated with lower rates of recurrence and survival benefits [5][6]. Recently, a myriad of clinical trials has been launched to investigate the efficacy of immune checkpoint inhibitors combined with neoadjuvant therapy [7][8][9]. The outcome of these clinical trials may significantly change the therapeutic landscape of MIBC patients as half of MIBC patients are not eligible to receive platinum-based neoadjuvant chemotherapy [10]. In patients receiving treatment with neoadjuvant therapy, pathological complete response (pCR, pT0N0) rates have been observed in 20% to 50% of cases [6][7][9]. While there is still room to develop more effective neoadjuvant therapies and increase pCR rates, avoiding surgery in bladder cancer patients who completely respond to neoadjuvant therapy is a continuing challenge faced by many urologic oncologists. Additionally, disease recurrence has been reported in a subset of patients initially diagnosed with pCR, highlighting the need to identify patients who present with occult metastasis at the time of surgery, as they could benefit from active surveillance and additional therapy to prevent disease recurrence. There is a critical need to identify those patients who can safely avoid surgery following neoadjuvant therapy, as well as those who need follow-up and additional therapy [11][12][13].

2. Current Precision Medicine-Approaches for the Treatment of Bladder Cancer Are Promising but Have Significant Drawbacks

To date, bladder cancer management decisions have been based on conventional histological features including tumor stage, lymph node status, and histology variant at the time of diagnosis. Half of patients treated with neoadjuvant therapy, however, do not respond to treatment, highlighting our current inability to accurately predict those patients who will respond to chemotherapy [6][7][9]. Pathological factors have been evaluated for their predictive value in the context of muscle-invasive bladder cancer [14]. Specifically, patients with pure urothelial carcinoma have ~11 times more chance to experience pathological complete response post-neoadjuvant therapy (NAT) compared to tumors with histological variants or mixed tumors. While pure urothelial carcinoma constitutes ~70% of cases of bladder cancer, the remaining cases are histologic variants or have mixed histological features [15]. This intratumor heterogeneity is a significant hurdle to any clinical decision-making involving best choice of treatment for patients with UBC [16].

Recent technological advances have allowed for efficient deep molecular profiling of bladder cancer tumors to support prediction of clinical outcomes and responses to therapy [17][18][19]. Transcriptomic profiling of biopsy and cystectomy specimens has, for instance, revealed distinct molecular subtypes of bladder cancer [18][20][21][22][23]. Similar to histology, molecular classification reveals important tumor heterogeneity with co-existence of luminal and basal subtypes within the same tumor in ~30% of cases [24][25]. However, while studies agree on gene expression signatures that identify each

molecular subtype, they have shown conflicting results with regards to prediction of response to chemotherapy. Two recent studies, including one meta-analysis of 16 transcriptomic datasets, showed no significant difference in response rates to chemotherapy between tumor subtypes [20][21]. Overall, these findings collectively support the fact that UBC is a multifactorial disease whose genomic, transcriptomic, and epigenomic diversity represent a significant challenge in treatment decision-making. Additionally, the high cost of such molecular analyses and the relatively long turn-around time for data collection and downstream bioinformatic interrogation are further obstacles for personalized medicine applications [20][21]. These limitations underscore the need to develop additional biological resources that can improve patient stratification and better predict response to chemotherapy.

3. Preclinical 2D and Patient-Derived Xenograft Models Bring Value to Drug Discovery but Have Limited Bedside Applications

The increasingly recognized complexity and heterogeneity of bladder cancer has posed a major challenge to predicting treatment response. New tumor models generated from patient's tumor specimens, such as primary cell lines and patient-derived xenografts, have gained attention for preclinical drug testing. Conventional two-dimensional (2D) culture of urothelial carcinoma (UC) cells [26] has traditionally been used for prediction of chemotherapeutic efficacy [27]. Over the years, a large number of bladder cancer cell lines has been established, recapitulating genomic and phenotypic heterogeneity of bladder cancer [28]. However, the majority of bladder cancer cell lines have been established from muscle-invasive and metastatic bladder cancer. While non-muscle invasive bladder cancer is the most common form of urothelial carcinoma, establishment of primary cell lines has not been successful [28][29]. Although 2D cell lines can expand rapidly and offer the possibility for high-throughput drug screening, they do not faithfully reproduce the 3-dimensional nature and cellular diversity of native bladder cancer. Compounding this, cancer-derived 2D cell lines typically exhibit genetic drift after multiple passages [30]. These limiting factors likely contribute to failure in predicting in vivo drug response in cancer patients using only 2D cell lines.

Patient-derived xenografts (PDX) is an approach whereby patient tumor fragments are implanted into immunocompromised mice to generate tumors that recapitulate genomic and phenotypical features of a patient's original tumor [31][32]. PDX have value in both better understanding tumor biology and evaluating the efficacy of FDA-approved anticancer therapies or novel targeted treatments [33]. Although PDX models present an exciting opportunity for improving predictive value of preclinical studies, there are several hurdles to their translation into the clinic. The lack of an immune system in the immunocompromised host makes PDX models inadequate for modeling immune response and testing immunotherapies. Further, engraftment rates tend to positively correlate with tumor grade, meaning that low-grade patient tumors may not lead to a high yield of viable mouse tumors [34][35]. Finally, engrafted tumors can take several months to grow. This is a critical drawback for their application in translational medicine as, in the neoadjuvant setting, treatment is usually initiated within 3-4 weeks from the time of diagnosis. An ideal tumor model would combine the rapid growth and high-throughput potential of 2D models with the faithful recapitulation of host tumor microenvironment provided by PDX platforms.

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