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New Drugs

Emerging therapeutic targets in bladder cancer

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ABSTRACT

Treatment of muscle invasive urothelial bladder carcinoma (BCa) remains a major challenge. Comprehensive genomic profiling of tumors and identification of driver mutations may reveal new therapeutic targets. This manuscript discusses relevant molecular drivers of the malignant phenotype and agents with therapeutic potential in BCa. Small molecule pan-FGFR inhibitors have shown encouraging efficacy and safety results especially among patients with activating FGFR mutations or translocations. mTOR inhibitors for patients with TSC1 mutations and concomitant targeting of PI3K and MEK represent strategies to block PI3K/AKT/mTOR pathway. Encouraging preclinical results with ado-trastuzumab emtansine (T-DM1) exemplifies a new potential treatment for HER2-positive BCa along with innovative bispecific antibodies. Inhibitors of cell cycle regulators (aurora kinase, polo-like kinase 1, and cyclin-dependent kinase 4) are being investigated in combination with chemotherapy. Early results of clinical studies with anti-CTLA4 and anti-PDL1 are propelling immune modulating drugs to the forefront of emerging treatments for BCa. Collectively, these novel therapeutic targets and treatment strategies hold promise to improve the outcome of patients afflicted with this malignancy.

Introduction

Urothelial bladder carcinoma (BCa) is a major global health challenge with an estimated 429,000 new cases resulting in 165,000 deaths annually [1]. In the United States, approximately 74,000 new cases will be diagnosed, and nearly 16,000 patients will die from bladder cancer in 2014 [2]. In males, BCa represents the fourth most frequent diagnosis of new cancers annually. Over the past two decades, there has been no significant improvement in survival of BCa with 5-year relative survival rates for locally advanced and metastatic disease of 33% and 5%, respectively [2].

The majority of bladder cancers are composed of urothelial carcinoma (90%) with the remaining less common subtypes including squamous cell carcinoma, adenocarcinoma, and small cell carcinoma. Seventy percent of the cases are diagnosed as non-muscle-invasive bladder cancer (NMIBC) with a favorable prognosis following transurethral resection and intravesical chemotherapy or immunotherapy with Bacillus Calmette-Guérin (BCG) [3]. Nevertheless, approximately 40% of these patients will progress to muscle-invasive disease at five years depending on tumor pathological features [4]. When considering the prognosis of muscle-invasive bladder cancer, even after optimal treatment with neoadjuvant chemotherapy and surgery, only 60% of these patients will be alive 5 years later due to distant recurrence [5]. This aggressive biological behavior coupled with limited therapeutic options results in a median survival of 15 months for patients with metastatic disease [6]. Therefore, there is an urgent need to improve outcomes with innovation or application of new treatments.

Advances in the understanding of the pathophysiology provided by comprehensive genomic profiling of BCa may drastically improve the outcomes for this malignancy [7]. The Cancer Genome Atlas (TCGA) uncovered recurring alterations in 32 genes and three distinct molecular subtypes of BCa providing the foundation for further investigation and drug development [7]. Prominent pathways altered in a significant fraction of BCa include the PI3K/AKT/mTOR pathway, the MAPK pathway, and chromatin regulatory genes. Novel therapeutic approaches with encouraging pre-clinical results and those undergoing early phase clinical development for

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muscle-invasive bladder carcinoma are discussed on this manuscript. The selection of therapeutic targets was based on the relevance of the pathways to emerging new treatments, and they were organized in the following groups: signal transduction pathway inhibitors, cell cycle regulation, heat shock proteins, and immunotherapy.

Signal transduction pathway inhibitors

Fibroblast growth factor signaling

Fibroblast growth factors (FGF), a family comprised of eighteen growth factors and four FGF-homologous factors, play an important role in several cellular processes including development, wound-healing, proliferation and angiogenesis [8]. These growth factors signal through four transmembrane glycoprotein receptors (FGFR1–4) that share a general structure of three extracellular immunoglobulin (Ig) domains, a transmembrane domain and an intracellular tyrosine-kinase domain. Ligand binding leads to receptor dimerization, phosphorylation of the cytoplasmic tyrosine kinase domain and activation of phospholipase C γ1 (PLCγ1), FGFR substrate 2 (FRS2), Ras/Raf/Mek/Erk, Jnk/Mapk, PI3K and STAT3 pathways [9]. FGF-1 and FGF-2 can also be internalized through receptor-mediated endocytosis and exert direct biological functions in the cytoplasm and nucleus [10]. The signaling complexity of the FGF/FGFR system relates to FGFs affinity to various FGFRs, isoforms of FGFRs with distinct ligand specificity and modulation of FGF by the sprouty family of proteins and FGF-binding proteins [11,12]. Another FGFR receptor has been described (FGFR5 or FGFR-like 1), but it does not have intrinsic tyrosine kinase activity and it might function as a decoy receptor inhibiting canonical FGFR signaling [13]. FGFRs gain-of-function mutations have a pivotal role on syndromes causing craniosynostosis (premature fusion of skull bones; Pfeiffer's and Apert's syndromes), Kallman's syndrome, achondroplasia (most common genetic form of dwarfism associated with FGFR3 mutations), and they have been documented in several malignancies including glioblastoma, multiple myeloma, head and neck, prostate, breast and bladder cancers [14–22].

The high frequency of FGFR genetic alterations encountered in urothelial carcinomas fostered significant interest in this pathway as a potential therapeutic target [22,23]. Results from TCGA documented multiple genetic lesions resulting in FGFR3 activation in 17% of muscle-invasive BCa [7]. These mutations are commonly located in exons 7, 10 and 15 encoding the extracellular domain of the receptor causing ligand-independent receptor activation [24]. Next-generation sequencing analysis of 126 cases of urothelial cancers revealed FGFR aberrations in 33% of the tumors [25]. FGFR3 was the most common receptor altered with activating mutations, amplification and fusions (FGFR3-TACC3) detected in 16%, 10% and 3% of the cases, respectively. In addition, overexpression of FGFR3 can be present in 40% of tumors without FGFR mutations [26]. A number of preclinical studies involving both bladder cancer cells lines and xenograft models of bladder cancer demonstrated the anti-proliferative activity of FGFR inhibitors and their ability to block FGFR-mediated signaling pathways [27–29]. Collectively, these results highlighted the potentially pivotal role of FGFR in urothelial carcinogenesis.

Small molecule inhibitors of FGFR 1, 2, 3 and 4 have shown encouraging results in bladder cancer. A phase I trial testing the oral pan-FGFR inhibitor JNJ-42756493 demonstrated a favorable toxicity profile with early signals of efficacy [30]. Thirty-seven patients with advanced solid tumors irrespective of their FGFR mutational status were treated during the dose escalation phase. Most of the adverse effects (AEs) were mild to moderate and included hyperphosphatemia (60%), asthenia (46%), dry mouth (30%), vomiting (22%) and constipation (27%). One patient developed grade 3 AST/ALT (aspartate aminotransferase/alanine aminotransferase) elevation classified as a dose-limiting toxicity. The drug also caused a dose-dependent increase in calcium, fibroblast growth factor 23 (FGF23), and phosphate coupled with a decrease in parathyroid hormone (PTH) that support the FGF/FGFR role in bone metabolism [31]. One patient with metastatic bladder cancer carrying the FGFR3-TACC3 translocation had a partial response, and another patient with renal pelvis tumor with FGFR2 truncation had a near complete response. Four additional patients achieved stable disease (breast cancer, lung cancer, and chondrosarcoma). Enrollment to the expansion cohort is ongoing (NCT01962532).

Another phase I study tested the pan-FGFR inhibitor BGJ398 specifically in patients with solid tumors carrying FGFR genetic alterations [32]. Dose-limiting toxicities observed among the ninety-four patients enrolled included grade 3 elevation of aminotransferases, grade 3 hyperphosphatemia, and grade 1 corneal toxicity. Other milder adverse effects were fatigue, decreased appetite, alopecia, and stomatitis. Frequent hyperphosphatemia (occurring in up to 78% of patients) was controlled with diet and phosphate-binding agents. Of note, four out of five patients with FGFR3-mutated urothelial carcinomas had tumor responses. Clinical activity was also observed in small cell lung cancer, breast cancer, and cholangiocarcinoma cases. An expansion cohort in bladder cancer with this compound is ongoing (NCT01004224). A third FGFR inhibitor (LY2874455) was evaluated in 36 patients with advanced solid tumors including 17 Asian patients [33]. Adverse effects (AEs) reported were gastrointestinal toxicity, hyperphosphatemia, and thrombosis. Dose-limiting toxicities were not observed, and dose expansion cohort is ongoing. Efficacy results have not been reported (NCT01212107).

In contrast to the encouraging results with specific FGFR inhibitors, multi-targeted tyrosine kinase inhibitors (TKIs) have not shown significant efficacy in BCa. Dovitinib, a TKI against VEFG and FGFR, was evaluated in 44 patients with advanced urothelial carcinomas without tumor responses even among patients with FGFR3 mutations [34]. The reasons for lack of activity is unclear, but may be related to non-selective pharmacological properties and potency of this compound. Nevertheless, further development of FGFR inhibitors might lead to effective strategies to treat BCa as single agents or in combination with chemotherapy.

Phosphatidylinossitol 3-kinase/v-akt murine thymoma viral oncogene homolog 1/mammalian target of rapamycin (PI3K/AKT/mTOR)

The PI3K/AKT/mTOR pathway is involved in cancer cell survival, motility and metabolism. Forty percent of urothelial carcinomas have genetic alterations of the PI3K/AKT/mTOR pathway. The spectrum of mutations include activating mutations of PIK3, AKT1 or inactivating deletions of critical regulators such as PTEN, TSC1 (tuberous sclerosis complex 1) and TSC2 [35–38]. Thus, multiple drugs have been designed to target this pathway (e.g. PI3K inhibitors, mTOR inhibitors, PI3K/mTOR dual inhibitors, AKT inhibitors, and PDK1 inhibitors).

Several compounds targeting individual or all isoforms of class I PI3K (i.e. p110α, p110β, p110γ) are in clinical development. The pan-PI3K inhibitor buparlisib (BKM-120) has been investigated in advanced solid tumors with partial responses observed in breast cancer and epithelioid hemangiothelioma [39]. Most frequent grade 3 and 4 AEs included rash, hyperglycemia, and increased transaminases. Based on these results and preclinical evidence of anti-proliferative effect in bladder cancer cells with PI3K blockade [40], buparlisib is being investigated as a second-line treatment for patients with metastatic urothelial carcinoma (NCT01551030).