Commentary

Muscle-Invasive Bladder Cancer: Advances in Molecular Substratification

Kevin Doello[1,2]†, Raquel Luque[1]†, Cristina Mesas[2,3], Consolación Melguizo[2,3,4] and José Prados[2,3,4]*

[1]Medical Oncology Service, Virgen de las Nieves Hospital, Spain
[2]Institute of Biopathology and Regenerative Medicine (IBIMER), Center of Biomedical Research (CIBM), University of Granada, Spain
[3]Department of Anatomy and Embryology, Faculty of Medicine, University of Granada, Spain
[4]Biosanitary Institute of Granada (Inst Invest Biosanitaria Ibs GRANADA), SAS-Universidad de Granada, Spain

***Corresponding Author:** José Prados. Institute of Biopathology and Regenerative Medicine (IBIMER), University of Granada, Tel: +34-958248819; Fax: +34-958246296

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Abstract

Urothelial vesical carcinoma (UVC) is the fourth most frequent in men and the ninth in women in developed countries. The 75% is non-muscle invasive disease and the remaining 25% is muscle-invasive disease which has worse prognosis and a five-year overall survival of 50%. The standard treatment of localized muscle invasive disease is neo-adjuvant chemotherapy and subsequent radical cystectomy with regional lymphadenectomy. In metastatic form, chemotherapeutic treatment has recently incorporated the immunotherapy with drugs like Pembrolizumab, Atezolizumab y Nivolumab. However, the current treatment is based on a classic pathological classification not always related to patient risk. During last years, we have gone in depth of UVC molecular knowledge, assessing molecular alterations in cellular pathways that are dysregulated in UVC and related to its progression and tumorigenesis. The cancer genome atlas (TCGA) classification distinguishes at this moment five subgroups with different molecular characteristics (luminal-papilary, luminal-infiltrated, luminal blue, basal-squamous and neuronal). These molecular signatures are related to patient prognosis and, so, they may have important implications in treatment. In this review we will go over the newest aspects of molecular classification of TGCA and systemic treatment.

Keywords

Urothelial Vesical Carcinoma; Molecular Signature; Immunotherapy

Introduction

Bladder cancer is the fourth most common in men and the ninth in women. It has an annual incidence of 30 cases per 100,000 inhabitants (in Southern and Western Europe) and an overall mortality of 11.3 per 100,000 inhabitants. Its histology in 80% of cases is urothelium, while in the remaining 20% have other histologies such as adenocarcinomas or neuroendocrine tumors [1]. Among the risk fac-

tors include smoking, exposure to anilines, dyes and various chemical compounds, germline mutations in detoxification genes (acetyltransferases) and infections by certain parasites (schistosome) [1]. The most frequent symptoms at diagnosis are irritative symptoms such as urgency, dysuria or incontinence and obstructive symptoms such as difficulty urinating, tenesmus and nocturia. The most characteristic sign is hematuria which appears between 80 and 90% of cases [1].

According to its locoregional extension, bladder cancer is classified as Ta or non-invasive papillary carcinoma, Tis or carcinoma in situ or flat tumor, T1 or tumor that invades the subepithelial conjunctive, T2, which invades muscularis propria, T3 that invades perivesical tissues, T4a, a tumor that invades the prostate or vagina and T4b, a tumor that invades the pelvic or abdominal wall. Regarding staging, it should be noted that in this case tumor stage IV is defined as a tumor that has positive tumor nodes (N+), a T4b (which invades the pelvic or abdominal wall) or distant metastasis (M1) [2]. The 5-year survival of localized bladder tumors (Ta, Tis or T1) is 80% with a local recurrence rate of 50%. The tumors located in the urothelium are the most frequent. In the case of locally advanced and metastatic tumors (T3, T4a and stage IV) it is 20%. At diagnosis, 85% of the tumors are confined to the bladder and 15% are disseminated [2].

Depending on the T and the staging, the bladder cancer handling is different. In Ta, Tis and T1 tumors, treatment is based on trans-urethral endoscopic resection and intraurethral instillations of BCG and mitomycin C [3]. T2 tumors are treated with radical cystectomy with Bricker reconstruction. Radical cystectomy can be avoided with an organopreservative protocol using radiotherapy and chemotherapy based on 5-fluorouracil and mitomycin C [4]. T3 and T4a tumors and occasionally T2 tumors undergo neoadjuvant chemotherapy based on cisplatin and gemcitabine. The neoadjuvant chemotherapy protocols reach up to 20% of complete responses. In case of a good response, radical surgery can be carried out [4]. Patients suffering from stage IV tumors (T4b, N + or M1) are treated as metastatic tumors with chemotherapy. The first line is based on carboplatin and gemcitabine.

In following treatment lines, treatments such as vinflunine or taxanes are proposed [4].

Immunotherapy in Urothelial Vesical Carcinoma

Immunotherapy (IT) has revolutionized the tumor strategy of different malignancies, such as lung cancer, clear cell renal carcinoma, melanoma and UVC. In this last, the use of IT is not a novelty since the intravesical administration of the attenuated vaccine against tuberculosis called Bacillus Calmette-Guérin was approved in the 90s of the 20th century for urothelial carcinoma of high grade non-invasive bladder [5]. We know that tumor cells are capable of evading the immune system through molecular signals that inhibit the immune response (IR). The control points PD1 (programmed cell death protein 1) and its ligand PDL1 (programmed death ligand 1) represent the inhibitory targets of the IR on which research on the CUV has focused. Pembrolizumab and nivolumab as well as atezolizumab, durvalumab and avelumab (antibodies against PDL1) have been approved by the US Food and Drug Administration and the first three by European Medicines Agency (EMA)I for patients progressing to platinum therapy [6]. Only Pembrolizumab and Atezolizumab have comparative studies against chemotherapy in this scenario. In the phase III study KEYNOTE 045, Pembrolizumab showed an increase in overall survival (OS) versus chemotherapy [7]. The same did not occur in the phase III study IMvigor211, in which Atezolizumab did not significantly increased OS against chemotherapy in patients with PDL1 expression> 5% in the inflammatory cell that infiltrates the tumor [8].

In the first line of treatment we do not have results of randomized studies against platinum schemes. However the non-comparative phase II studies conducted in the non-candidate population of cisplatin show results favoring the use of these agents for efficacy and tolerance against the carboplatin gemcitabine combination. Thus, EMA authorized the use of pembrolizumab and atezolizumab in the first line for patients not candidates for cisplatin with positive PDL1

expression. Currently, the expression of PDL1 has contradictory data for the selection of the population that would respond to inhibitors of these immune control points. There is no standardized method for evaluating the expression of PDL1 which has been determined in the inflammatory cell, in the tumor cell or in both. In addition, PDL1 show high expression heterogeneity in tumor and metastasis [9]. New studies that are underway will answer these questions.

Molecular Classification of Urothelial Vesical Carcinoma

Currently, UVC treatment is based on histological and clinical data which do not select the population at risk or the patients who benefit from a complementary or palliative treatment. The TCGA is a project that began in 2005 with the purpose of deepening the molecular knowledge of cancer. It has generated the genomic map of 33 types of cancer, including UVC [10]. Before the TCGA, there have been other classifications. The MD Anderson group distinguished three subtypes in 73 musculoinvasive CU samples, including only 10% of metastatic patients: basal, characterized by p63 activation, squamous differentiation and high expression of EGFR, as the basal subtype of breast cancer, luminal, enriched with epithelial markers and characterized by mutations of FGFR3 and p53like, considered resistant to chemotherapy. The basal subtype had a shorter survival. In 2014, the first molecular characterization of the UVC of the TCGA was published [11]. In this study, tumor samples from 131 patients with muscle-invasive UC without distant lymph node or metastatic involvement and without chemotherapy treatment were analyzed. The study includes data on somatic DNA alterations, chromosomal rearrangements and viral integration, mRNA expression, protein expression and analysis of the main intracellular pathways involved, as well as possible targeted treatments, an identifies four clusters. The Cluster I or papillary is characterized by papillary morphology, mutations of FGFR3, gain of copies of FGFR3 and high expression of FGFR3. Therefore this type of tumor could be treated with FGFR inhibitors. Both Cluster I and Cluster II present high expression of HER2. They

resemble the luminal A of breast cancer and characterize by the expression of epithelial markers. Cluster III or basal / squamous like is similar to basal like breast and squamous cancer of the head and neck and characterize by expression of EGFR and cytokeratins. Cluster IV shows mesenchymal differentiation. In addition, a high rate of somatic mutations and alterations in pathways involved in the regulation of cell cycle and chromatin and in the pathway of kinases were detected. In 2017, the update of this analysis was published with a cohort of 412 samples, including localized patients and metastatic patients, who have not received chemotherapy treatment previously. This publication adds the study of new mutations, mutational load and neoantigen including five signatures of mutations [12]. Integrating all this information, five subtypes are distinguished. The papillary luminal subtype (35% of the samples) which is characterized by papillary morphology, mutations, fusions and amplifications of FGFR3, more indolent course and low response to cisplatin. The infiltrated luminal subtype (19%) is characterized by its low purity showing lymphocytic infiltrate, high expression of epithelial-mesenchymal transition markers and myofibroblasts, as well as being p53 wild type. It corresponds to Cluster II of the 2014 classification and obtains good response to immunotherapy and poor to chemotherapy with cisplatin treatment. The luminal subtype (6%) shows high expression of luminal markers such as KRT90 and SNX31. The basal / squamous subtype (35%) is more frequent in women, shows squamous differentiation and is usually associated with carcinoma in situ. This subtype presents high expression of cytokeratins and immunological markers such as CTLA4 and inflammatory immune infiltrate. In addition, it shows TP53 mutations and responses to IT and cisplatin-based chemotherapy.

Finally, the neuronal subtype (5%) is characterized by the expression of neuroendocrine and neuronal markers, loss of TP53 and RB1. It should be treated with platinum-type chemotherapy-etoposide. Recently, the results of the analysis of a cohort with 2411 samples of patients with non-muscle-invasive UC, localized muscle invasive CU and metastatic UC have been published [13]. It is an attempt to unify the different classifications. They describe 6 molecular subtypes

(MC1-6) that they denominate BOLD (BCLA subtypes of large meta-cohort) and that they correlate with the subtypes of the rest of classifications. In this way MC1 corresponds to the neural-like subtype (NEURAL) and is similar to the neuronal subtype of the TCGA. MC2 is the luminal like (LUM). MC3 is the papillary like (PAP), similar to the papillary luminal of the TCGA. MC4 or HER2-like (HER2L) similar to the luminal of the TCGA. MC5 / squamous cell carcinoma like (SCC), which corresponds to the squamous basal TCGA. And MC6 or mesenchymal like (MES) which would correspond to the luminal infiltrate of TCGA. This corroborates the existence of three luminal / epithelial subtypes like: PAP, LUM, HER2, a basal / squamous subtype, a neural subtype, and a claudin -low / stem like subtype which is the mesenchymal MES. Classification into molecular subtypes has a prognostic value and differentiates patients with more aggressive tumors from patients with favorable course tumors such as the PAP subtype. In addition it also has therapeutic implications. The MES subtype would be resistant to cisplatin-based chemotherapy. The subtype HER2L presents a high mutational and neoantigenic rate and is the one that benefits the most from Atezolizumab in the phase II study IMvigor 210 [14]. The PAP subtype would be a candidate for FGFR inhibitors. For this reason, the classification in molecular subtypes has an important clinical relevance and should be incorporated into the studies in UVC.

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