Editorial

Neoadjuvant cisplatin-based chemotherapy in "primary" and "secondary" muscle-invasive bladder cancer—is it a surrogate for molecular subtypes?

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Perioperative cisplatin-based combination chemotherapy is a first-line treatment strategy for muscle-invasive bladder cancer (MIBC) patients with or without metastasis. According to current European Association of Urology (EAU) guidelines, the use of neoadjuvant chemotherapy (NAC) is strongly recommended to patients with clinical T2–T4a and N0M0 disease (1). However, existing data show that NAC provides only an 8% absolute survival benefit at five years, which means that 12 patients have to be treated with NAC to avoid one death in five years (2). This demonstrates that only a smaller group of patients benefit from NAC treatment. This survival benefit is restricted to pathological responders, who show partial or complete response. In addition, novel effective immunotherapy agents are now available for cisplatin resistant and cisplatin ineligible MIBC patients. Therefore, there is an urgent and unmet need for biomarkers in order to predict response to cisplatin chemotherapy.

In their study Pietzak *et al.* divided patients into groups of "primary" MIBC (patients who had MIBC at first diagnosis) and "secondary" MIBC (who were diagnosed with a non-muscle invasive bladder cancer and progressed to MIBC) and found that secondary MIBC patients experienced lower survival rates after NAC treatment compared to patients with primary MIBC (3). In addition, they demonstrated that patients that do not exhibit a pathologic response to NAC had inferior survival rates compared to patients who were only treated by radical cystectomy without NAC. This suggests that patients who are not responsive to cisplatin have a better chance of survival with upfront cystectomy without NAC. This observation is important and further highlights the need for prediction of cisplatin therapy.

Urinary bladder cancer in most cases manifests as urothelial carcinoma which is a heterogeneous disease regarding its morphological and histological appearance as well as its clinical behavior. About 70% of BCs are non-muscle-invasive (NMIBC) at first presentation, while 30% of patients already have muscle-invasive disease (MIBC). These two groups of patients show characteristic differences regarding their clinical behavior as well as morphological, histological and molecular features. NMIBC patients are usually treated with transurethral resection and have an excellent prognosis with a survival rate of over 90% after five years. NMIBCs often recur but rarely progress. In contrast, MIBC patients have a survival rate of only 50% after five years. MIBC patients are usually treated with radical cystectomy and perioperative, adjuvant or NAC. NMIBCs mostly appear as papillary disease while MIBC predominantly shows higher tumor burden and in almost all cases a high-grade morphology with more solid growth patterns [for the usual/not-otherwise specified (NOS) type] or variant differentiation as for example micropapillary, squamous or plasmacytoid patterns which can be detected in up to one third of cases and are associated with

worse outcome (4). The fact that NMIBCs relatively rarely progress to MIBC suggests different molecular pathomechanisms for these two clinically different patient groups. Early studies identified typical genetic alterations for NMIBC which are less frequently present in MIBC further confirming the different nature of these tumors. NMIBCs show an overall lower mutational load with high frequencies of 9p chromosomal deletion (*CDKN2A* loss) as well as *FGFR3* and *HRAS* alterations. In contrast, MIBC exhibit a high rate of genetic instability with abundant *TP53* and *RB1* mutations but less frequent *FGFR3* and *CDKN2A* alterations (5).

In the last few years high throughput sequencing and gene expression analyses provided a never before seen insight into the molecular background of cancer. In bladder cancer, hierarchical cluster analyses of gene expression data distinguished different molecular subtypes in muscle-invasive urothelial cancer, as for example the "luminal" and "basal" subtypes which were named after their parallels in breast cancer (6,7). Basal tumors can be characterized by high expressions of mesenchymal markers and EGFR, while luminal bladder cancers typically express epithelial markers and show higher *FGFR3* alteration rates (7). In addition, a "p53-like" subtype has been distinguished with both luminal and basal gene expressions and a gene signature activated by wild-type p53. However, a later immunohistochemical study revealed that the characteristic p53-like markers were almost exclusively expressed in the stromal cells (fibroblasts, smooth muscle cells, immune cells) but not in the cancer cells themselves. Therefore, the p53-like gene signature is most probably a result of stromal contamination and therefore does not represent an intrinsic subtype of bladder cancer (8). In further analyses, the The Cancer Genome Atlas (TCGA) consortium comprehensively analyzed the molecular background of 412 MIBCs (9). This study supported the existence of luminal and basal subtypes and additionally identified the smaller subgroup of "neuroendocrine-like" tumors with a very unfavorable prognosis. Furthermore, the luminal subtype was subdivided into "luminal papillary", "luminal infiltrated" and "luminal" groups. Based on molecular features both at the DNA and RNA level, the luminal papillary subtype shows the highest similarity to NMIBC, which suggests that tumors progressed from NMIBCs are enriched in the luminal papillary subtype. According to a large study on MIBC patients with or without NAC treatment, none of the luminal subtypes benefited from chemotherapy and only MIBC patients with basal molecular subtype gained any survival benefit from NAC (10). In addition, Pietzak and co-workers in the present study found that patients with secondary MIBC have lower radiographic response rates and shorter survival compared to primary MIBC, suggesting that secondary MIBC patients are more likely to be chemotherapy-resistant (3). Against this background, it seems plausible that the secondary MIBCs in Pietzak's study mainly resemble tumors of the luminal subtypes—most probably the luminal papillary subtype—which is known to be cisplatin-resistant. However, in their study the authors state that their primary and secondary groups did not overlap with molecular subtypes when analyzed in the discovery cohort. Comparing the mutation pattern between Pietzak's primary and secondary MIBC groups in the validation cohort, we may have observed differences between typically affected genes. *TP53* and *RB1* mutations—which are known to be enriched in basal subtype - are more frequent in primary MIBC (42% *vs.* 69% for *TP53*, 17% *vs.* 31% for *RB1*) while *CDKN2A* and *FGFR3* alterations which are known to be more abundant in the luminal subtype were more frequent in secondary MIBC (17% *vs.* 25% for *CDKN2A*, and 7% *vs.* 25% for *FGFR3*). Interestingly, when mutational frequencies are considered in the combined cohort (including both the retrospective discovery and prospective validation cohort), these characteristic differences in mutational frequencies disappeared. These marked differences in the mutation frequencies between the two cohorts may challenge the representative nature of the discovery cohort and might explain the lacking difference in the distribution of molecular subtypes between the primary versus secondary MIBC in the discovery cohort. As molecular subtypes as such have not been assessed in the prospective validation cohort, we cannot exclude a possible association of molecular subtypes with primary and secondary MIBC. Based on these, in our opinion the difference of NAC sensitivity between primary and secondary MIBC may be related to their different intrinsic molecular subtype. If so, dichotomization into primary and secondary MIBC might be used as a surrogate/indicative marker for the classification into luminal and basal subtypes and therefore might be used to predict cisplatin-sensitivity in bladder cancer. This would be of great clinical relevance as current subtype classifications are based on transcriptome sequencing with the parallel consideration of mRNA expressions of >3,000 genes which in its present form is too complex for routine clinical use.

In further large-scale cancer characterization efforts, the so-called pan-cancer analyses aim to compare genomic and cellular alterations across various tumors, which allows for the observation of fundamental differences and similarities between distinct tumor entities. This approach has allowed deciphering the patterns of somatic mutations caused by different mutational processes and resulted in the identification of 30 validated mutational signatures. The etiology of some of these mutational signatures has already been attributed to endogenous or exogenous mutagenic processes. There are mutational signatures found to be associated with exposures to ultraviolet (UV) light, aflatoxin, aristolochic acid, alkylating agents or tobacco smoking while others are associated with impaired mismatch or double-strand-break repair functions. In accordance, a mutational signature related to UV exposure was observed in malignant melanoma and mutational signatures associated to tobacco smoking were found in lung cancer. Surprisingly, despite smoking is known to be a significant risk factor for urothelial bladder cancer, typical smoking-related mutational signatures were not found in MIBC. On the other hand, according to the results of the TCGA II study on bladder cancer, *ERCC2*-related mutations were characteristic for one of the four mutational signature groups found in MIBC. In addition, the frequency of *ERCC2* signature mutations was associated with smoking, suggesting that smoking may influence the mutational landscape of bladder cancer by provoking an *ERCC2*-related mutational pattern (9). In the study of Pietzak *et al.*, *ERCC2* mutations were significantly enriched in patients with primary compared to secondary MIBC (17% *vs.* 0%). ERCC2 (ERCC Excision Repair 2, TFIIH Core Complex Helicase Subunit) is known to play a role in the nucleotide excision repair (NER) pathway. Chemotherapy agents such as cisplatin disrupt the DNA structure, which is recognized and repaired by the NER system. Urothelial cancer carries somatic mutation of *ERCC2* gene with a relative high frequency of 6–18%.

The *ERCC2* genetic alterations have formerly found to be associated with therapeutic response to NAC (11). Van Allen *et al.* performed whole-exome sequencing in 50 NAC treated MIBC patients (25 responders *vs.* 25 non-responders) in order to identify somatic mutations that occur preferentially in responders. *ERCC2* inactivating mutations were found to be the only genetic alterations to be significantly enriched in responders (35% in responders *vs.* 0% in non-responders). These results could be validated in a similar sized independent validation cohort showing *ERCC2* mutations in 40% of responders compared to 7% of non-responders (12). Pietzak and co-worker's results indirectly support the predictive role of ERCC2 in cisplatin therapy as its mutations were significantly enriched in primary MIBC patients who had a better response to chemotherapy compared to secondary MIBC. In contrast, Gronendijk *et al.* found *ERCC2* mutations in 16% of responders compared to 6% of non-responders which did not reach the significance level (13). In a further discussion of these conflicting results, it has been highlighted that the two *ERCC2* mutant and non-responder patients received carboplatin and not cisplatin which may account for discrepant findings (12,14). Recent functional analyses demonstrated that nearly all clinically observed *ERCC2* missense mutations were able to attenuate normal cellular NER and consequently increase sensitivity to cisplatin (15). In summary, *ERCC2* alterations are associated with smoking, they are more common in primary MIBC and they are clearly associated with a better response to cisplatin therapy. Therefore, ERCC2 may be a valuable marker for the prediction of NAC efficacy in MIBC, however, it seems to have a high positive predictive value but low negative predictive value meaning that an ERCC2 test could identify potential responders with a high reliability but at the same time would miss a relative high number of potential responders. Therefore, testing of ERCC2 status may be used in combination with other markers rather than alone to select MIBC patients potentially eligible for cisplatin therapy.

In conclusion, current changes in the therapeutic landscape of bladder cancer call for methods of efficacy prediction of perioperative cisplatin-based chemotherapy in order to guide therapy decisions in a more individualized manner. The study of Pietzak and co-workers shows that the two groups of MIBC and molecular patterns are linked which might provide clues for the improvement of clinical decision-making.

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