Editorial Commentary

Adjuvant chemotherapy in bladder cancer patients with histological variants: time to change the approach?

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Bladder cancer (BCa) is a common malignancy, with about 81,190 estimated new cases and 17,240 estimated deaths in the United States in 2018 (1). Neoadjuvant cisplatin-based combination chemotherapy (NAC) followed by radical cystectomy (RC) with bilateral pelvic lymph node dissection is currently considered the standard of care in muscle-invasive bladder cancer (MIBC) patients (2). However, 5 years survival after surgery is approximately 50% (3). In this regard, adjuvant cisplatin based-chemotherapy (AC) improves survival outcomes and should be administered in medically fit, NAC naïve patients with pT3/4 and/or positive nodes diseases at RC (2).

A recent meta-analysis of eleven randomized clinical trials has shown significantly improved progression free survival [hazard ratio (HR) 0.64; 95% CI, 0.49–0.85] and overall survival (OS) (HR 0.79; 95% CI, 0.68–0.92) in patients treated with AC compared to those treated with RC alone (4). These trials, however, focused on pure urothelial carcinoma (UC) only. On the other hand, BCa encompasses a wide spectrum of malignancies, including thirteen UC varieties and several non-urothelial types (5,6). Each of these histopathological entities has shown to be associated with different survival outcomes, probably due to the underlying presence of specific mutational landscapes (5,7-9). Given the heterogeneous behavior of these conditions, a "one size fits all" approach in the therapeutic setting might not be ideal (9). Moreover, considering that from one tenth to one third of BCa patients are diagnosed with a non-pure UC, a tailored treatment might have a big impact in the overall management of these conditions (7,8,10,11).

Different studies have shown that there is an unmet need in the definition of the optimal approach after RC in the subset of patients with MIBC and a non-pure urothelial type disease (9-11). Berg *et al.* assessed the impact of AC vs initial observation after RC in AC candidates affected by pure UC and histological variants (12). The aim of the study was to assess OS based on the time of RC to the date of death in the two treatment groups. UC variants analyzed in the study included micropapillary and sarcomatoid differentiation, squamous cell carcinoma (SCC), adenocarcinoma, and neuroendocrine tumors, which are some of the most common subtypes of BCa (9,10,13). Using the National Cancer Data Base, 15,397 patients with nonmetastatic localized BCa and positive lymph nodes (T2N+) or locally advanced stage (≥ T3N0/N+) were included in the analysis, since it is believed that these patients benefit the most from AC. Patients who underwent NAC were excluded. Of note, patients who received AC after 90 days from surgery were included into the initial observation cohort, considering them under a salvage chemotherapy regimen. Overall, 3,053 patients of 13,210 (23%) with a pure UC and 430 of 2,187 (24%) with a non-pure UC subtype underwent RC and subsequent AC. Patients treated with AC were younger (64 *vs.* 70 years, P<0.001) and with fewer comorbidities (Charlson Comorbidity Index 0=74% *vs.* 67%, P<0.001) compared to those who underwent observation. At the multivariable analysis, the use of AC was associated to a benefit in OS in patients with pure UC (HR 0.87; 95%

CI, 0.82–0.91; P<0.001) or micropapillary differentiation (HR 0.87; 95% CI, 0.52–1.14; P=0.04) (4). On the other hand, all the others achieved similar OS outcomes in both studied cohorts. In a sensitivity analysis, patients with positive lymph nodes only (T2N+, T3N+, and T4N+) affected by adenocarcinoma, sarcomatoid differentiation, neuroendocrine tumors of the bladder, and UC obtained a significantly better OS benefit in the AC treatment group rather than in the initial observation group.

Taken together, these results underline that non-pure urothelial MIBC is predominantly not sensible to the current therapeutic regimens used in AC and that patient's performance status does not significantly influence OS. Moreover, although in previous studies lymph-node positivity has not clearly shown to drive a specific aggressive potential *per se* (14), BCa variants with prevalent node spread might bear diverse biological features and increased susceptibility to chemotherapeutic regimens. This hypothesis is supported by the results of a recent analysis by Kaushik *et al.* (11) regarding the role of AC in a group of 18 patients with small cell carcinoma of the bladder. The authors of this study found a statistically significant difference in terms of lymph node positivity in patients treated with AC (61% *vs.* 28%; P=0.01), who furthermore presented a superior 5 year-OS and cancer specific survival (CSS) compared to the AC naïve group.

This investigation from Berg *et al.* confirms several previous findings. Mitra *et al.* (15), in a recent multi-institutional study, analyzed 41 patients with micropapillary urothelial carcinoma (MUC) treated with AC, who obtained improved recurrence free survival and OS (P<0.01) from different AC regimens. The lack of a benefit in survival outcomes from AC in the SCC, the sarcomatoid differentiation and the adenocarcinoma is aligned with previous discoveries and underlines the limited effectiveness of chemotherapy regimens in these aggressive entities (16-18). Conversely, the absence of a significant improvement from AC in OS in the neuroendocrine variant is in contrast with previous results, which have highlighted the chemosensitive nature of this histology, both in the neoadjuvant and the adjuvant setting (17).

The study from Berg *et al.* is not devoid of limitations. First, the examined cohort includes patients treated between 2004 and 2015. Over this time frame, criteria, terminology and clinical understanding of UC variant diagnosis have been evolving (19). These aspects might have influenced the ability and the sensibility of pathologists in the histology description, resulting in either an over- or an underreporting. Second, the lack of a centralized pathologic review has been associated with a reduced identification of variant histologies. This aspect is probably related to the under-reporting of variant histology in community practice, due to frequent interobserver variability and to the rarity of these entities, whose identification results consequently challenging for not adequately trained pathologists (19-24). Third, the retrospective nature of this study addresses once again the chance of a misclassification bias and of other inherent drawbacks associated with this study approach. Fourth, the incomplete reporting and the heterogeneity of the AC regimens might mislead the interpretation of results. A sub stratification per type of chemotherapy regimen might help to identify better performing drug combinations. Fifth, this study lacks insight about molecular features, which are increasingly demonstrating a potential role in the diagnostic workup, prognosis definition and treatment selection (18,25). Due to these limitations, it is not possible to infer generalizable conclusions from this investigation.

Nonetheless, we acknowledge that this paper gives an overview on the effects of systemic therapy after RC on a group of poorly considered entities, using a relatively consistent number of patients. Moreover, it raises awareness on the need to further clarify the effects of AC in BCa variants and to better investigate other combinations of treatment after RC in order to reduce morbidity and optimize oncologic outcomes.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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