Editorial Commentary

Should every patient with muscle-invasive bladder cancer receive neoadjuvant chemotherapy?

Moritz Maas, Arnulf Stenzl

Department of Urology, Eberhard-Karls-University, Tübingen, Germany

Correspondence to: Arnulf Stenzl. Department of Urology, University Hospital Tuebingen, Hoppe-Seyler-Straße 3, Tübingen 72076, Germany. Email: urologie@med.uni-tuebingen.de.

Provenance: This is an invited article commissioned by Section Editor Xiao Li (Department of Urology, Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research & Nanjing Medical University Affiliated Cancer Hospital, Nanjing, China).

Comment on: Lyon TD, Frank I, Sharma V, *et al.* A risk-stratified approach to neoadjuvant chemotherapy in muscle-invasive bladder cancer: implications for patients classified with low-risk disease. World J Urol 2018. [Epub ahead of print].

Submitted Feb 07, 2019. Accepted for publication Mar 01, 2019.
doi: 10.21037/tau.2019.03.03
View this article at: http://dx.doi.org/10.21037/tau.2019.03.03

The use of cisplatin-based neoadjuvant chemotherapy (NAC) for all patients with muscle-invasive bladder cancer (MIBC) is recommended by current guidelines (1,2). However, the study of Bhindi *et al.* suggest, that patients not responding to NAC show an inferior survival than a comparable control group (3). Furthermore, only 20–38% of the patients exposed towards NAC show a histopathological response (4). Taking these aspects and the known chemotherapy-related toxicity into consideration leads both, providers and patients, to the question whether the potential benefits of NAC outweigh its disadvantages.

Until today, there are only few clinical decision tools to identify patients profiting from NAC. Histopathological studies, e.g., Pokuri *et al.* and Fleischmann *et al.* identified a high proliferation rate in TUR-BT specimen and the presence of pure urothelial histology as predicting factors for NAC-responding (5,6).

On the other hand, in 2014 the MD Anderson group of Culp *et al.* proposed a more clinical orientated evaluation scheme dividing MIBC patients into a low risk group on the one hand and a high-risk group on the other hand to identify those patients who profit of a NAC before RC (7).

Patients were considered high risk when showing at least one of the following aspects: variant histology, lymphovascular invasion, cT3b–4a disease or hydroureteronephrosis. The authors suggest NAC before cystectomy for patients showing a high-risk profile as they observed a 30–40% risk of occult lymph node-positive disease in this collective. Patients classified as low risk on the other hand should receive an immediate cystectomy without a previous NAC. As this collective only shows a 10% risk of lymph node positive disease and a 5-year cancer-specific survival of 82.7% the potential avoidance of chemotherapy associated toxicity has been seen by the authors.

The recently published study of Lyon *et al.* tries to validate these published risk criteria and investigate the outcomes of patients classified as LR and treated with Cx without NAC (8). This group is of particular interest as pathological upstaging is frequent (9,10) and peri- or postoperative complications may lead to a performance status excluding the patient from a platinum-based chemotherapy.

The authors could validate the proposed clinical risk groups of the MD Anderson group as HR patients experienced a significant lower 5-year CSS than LR patients (50% *vs.* 68%).

The reported 5-year CSS in LR patients treated with immediate RC without NAC was 68%, which is lower than the reported 5-year CSS of the MD Anderson group (83.5%) and data from other institutions (e.g., Moschini *et al.*: 77.4%) (7,11). In their patient cohort of LR patients treated with immediate RC without NAC, 52 % had a non-organ confined disease. This rate is similar to data from the group of von Runstadt *et al.* [46.9% (12)] and Culp *et al.* [49% (7)] whereas Moschini *et al.* report a rate of 70.6% (11)

upstaging after RC.

Only 14% of the patients, initially classified as LR and upstaged postoperative, received a platinum-based adjuvant therapy (AC), whereas 14% were not able to receive it due to peri- or postoperative events. The number of patients not receiving platinum-based chemotherapy might even be higher as Lyon *et al.* suspect a miss-classification of patients in the category "not receiving Chemotherapy by provider/ patients choice" caused by the retrospective nature of their study (8).

The authors present solid data from their cystectomy-cohort. The reported rates of non-organ confined disease is similar to other published cohorts. Especially remarkable are the 14% of patients not able to receive platinum-based AC due to peri- or postoperative complications. Even if this seems low, the authors correctly suspect an underrating caused by the retrospective nature of the study. Following these results, they suggest that all patients with MIBC should receive platinum-based chemotherapy instead of offering it to HR patients only as proposed by the MD Anderson group.

Even if recommended by the current guidelines, the use of platinum-based chemotherapy in patients with MIBC remains underutilized. Many of the patients and providers seem to prefer an immediate RC followed by a potential AC if histopathological classification requires this. The current study by Lyon *et al.* shows that following of this strategy at least 14% of initially LR classified patients get excluded from receiving platinum-based therapy, a number which is probably biased by the retrospective nature of the current study.

Heeding the presented data of this study, the proposed conclusion, that every patient with MIBC should receive NAC is comprehensible. However, it remains a challenge to identify the 30–40% of patients profiting from NAC to avoid chemotherapy-associated toxicity and delay for those patients not profiting. Clinical classification systems as these mentioned above might be a potential evaluation tool, on the other hand recently published data evaluating the molecular subtypes are promising approaches for the future (13).

As various studies evaluating the potential of checkpoint inhibition in the neoadjuvant setting for bladder cancer are emerging, it will furthermore be necessary to establish a decision guidance tool to separate patients with MIBC into these profiting from checkpoint inhibition most and those who take advantage of platinum-based therapy. Furthermore, the particles not responding to NAC (and eventually checkpoint inhibitors) need to be scrutinized.

Acknowledgments

None.

Footnote

Conflicts of Interest: A Stenzl is a member of the advisory board for Ipsen Pharma, Roche, Janssen, Alere, Bristol-Myers Squibb, Stebabiotech and Synergo. Furthermore, he declares a conflict of interest for Sanofi-Aventis, CureVac and Astellas. M Maas has no conflicts of interest to declare.

References

1. Alfred Witjes J, Lebret T, Comperat EM, et al. Updated 2016 EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer. Eur Urol 2017;71:462-75.
2. Clark PE, Spiess PE, Agarwal N, et al. NCCN Guidelines Insights: Bladder Cancer, Version 2.2016. J Natl Compr Canc Netw 2016;14:1213-24.
3. Bhindi B, Frank I, Mason RJ, et al. Oncologic Outcomes for Patients with Residual Cancer at Cystectomy Following Neoadjuvant Chemotherapy: A Pathologic Stage-matched Analysis. Eur Urol 2017;72:660-4.
4. Zargar H, Espiritu PN, Fairey AS, et al. Multicenter assessment of neoadjuvant chemotherapy for muscle-invasive bladder cancer. Eur Urol 2015;67:241-9.
5. Pokuri VK, Syed JR, Yang Z, et al. Predictors of Complete Pathologic Response (pT0) to Neoadjuvant Chemotherapy in Muscle-invasive Bladder Carcinoma. Clin Genitourin Cancer 2016;14:e59-65.
6. Fleischmann A, Thalmann GN, Perren A, et al. Tumor regression grade of urothelial bladder cancer after neoadjuvant chemotherapy: a novel and successful strategy to predict survival. Am J Surg Pathol 2014;38:325-32.
7. Culp SH, Dickstein RJ, Grossman HB, et al. Refining patient selection for neoadjuvant chemotherapy before radical cystectomy. J Urol 2014;191:40-7.
8. Lyon TD, Frank I, Sharma V, et al. A risk-stratified approach to neoadjuvant chemotherapy in muscle-invasive bladder cancer: implications for patients classified with low-risk disease. World J Urol 2018. [Epub ahead of print].
9. Turker P, Bostrom PJ, Wroclawski ML, et al. Upstaging of urothelial cancer at the time of radical cystectomy: factors associated with upstaging and its effect on outcome. BJU Int 2012;110:804-11.
10. Svatek RS, Shariat SF, Novara G, et al. Discrepancy

between clinical and pathological stage: external validation of the impact on prognosis in an international radical cystectomy cohort. BJU Int 2011;107:898-904.
11. Moschini M, Soria F, Klatte T, et al. Validation of Preoperative Risk Grouping of the Selection of Patients Most Likely to Benefit From Neoadjuvant Chemotherapy Before Radical Cystectomy. Clin Genitourin Cancer 2017;15:e267-73.
12. von Rundstedt FC, Mata DA, Kryvenko ON, et al. Utility of Clinical Risk Stratification in the Selection of Muscle-Invasive Bladder Cancer Patients for Neoadjuvant Chemotherapy: A Retrospective Cohort Study. Bladder Cancer 2017;3:35-44.
13. Seiler R, Ashab HAD, Erho N, et al. Impact of Molecular Subtypes in Muscle-invasive Bladder Cancer on Predicting Response and Survival after Neoadjuvant Chemotherapy. Eur Urol 2017;72:544-54.

Cite this article as: Maas M, Stenzl A. Should every patient with muscle-invasive bladder cancer receive neoadjuvant chemotherapy? Transl Androl Urol 2019;8(Suppl 3):S274-S276. doi: 10.21037/tau.2019.03.03

