Editorial Commentary

The risk of oversimplification in risk-stratification of neoadjuvant chemotherapy-responses in muscle invasive bladder cancer

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Background

The authors, Lyon *et al.*, analyzed 1,931 patients undergoing radical cystectomy (RC) for muscle invasive bladder cancer (MIBC) at the Mayo clinic, with the intention to evaluate a suggested response stratification of MIBC-patients in terms of treatment success for neoadjuvant chemotherapy (NAC) (1). The concept of risk stratification in low risk (LR) and high risk (HR) patient cohorts had been proposed by a clinical research group at MD Anderson, for evaluating which patients could be offered NAC and which patients could be presented with an option of upfront RC (2). The MD Anderson investigators suggested utilizing NAC in HR patients only and further suggested LR patients to receive immediate RC and an option of adjuvant chemotherapy.

Definitions of HR and LR patients

Culp *et al.* defined HR and LR patients by following combination of clinical and histopathological parameters:

- HR: hydroureteronephrosis, lymphovascular invasion (LVI), cT3b–4a disease, or variant histology;
- LR: lack of hydroureteronephrosis, lack of lymphovascular invasion (LVI), cT2a–T3a disease, isolated urothelial histology.

Problems with the suggested risk criteria

The main problem is in the clinical T-staging. Two aspects should be noted, firstly the problems in establishing the genuine cT-stage through histopathological analysis of the TURb-specimens. Understaging is a real clinical problem of which there still are no robust and reliable methods to substantially narrow the wide discrepancy between cT-stage and pT stage, even if establishment of presence or absence of LVI is beneficial as a valuable tool for risk stratification (3,4). Secondly, the question of hydroureteronephrosis, in which this problem is nothing but a moving target. To statically establish, at the early time point of primary investigation, that a patient is LR (lack of hydroureteronephrosis for instance as a suggested criterion) can quickly switch to a status of hydroureteronephrosis until the day of planned RC. What would then be the action? New MDT? NAC-treatment after all? More delays and more agony for the patient?

The main clinical problem

The efficacy of cisplatin-based NAC in urothelial MIBC, in terms of improved long term overall survival (OS), was established after the results from some well performed randomized prospective trials exploring this treatment option (5-7), also at 10 years of median observation (8), and has further led to national as well as international guidelines recommending NAC in fit patients (9). The main clinical problem is yet to identify, early in the clinical course, responders and non-responders to NAC, and to

adapt proper treatment/non-treatment algorithms following that kind of stratification. This approach aims at actually avoiding to offer NAC to non-responders. Approximately 60% of patients in larger cohorts can be considered as non-responding to NAC (6), and these non-responding patients are certainly at risk for progression during 2.5–4 months of practically ineffective treatment (the time-frame dependent on choice of NAC-treatment and number of cycles). In addition, there is a HR of grade 3 or chemotherapy-related toxicity (approx. 35%) (5,6), affecting both the wellbeing as well as the morbidity of the treated patients.

Results from the Nordic cystectomy trials 1 and 2 and the ensuing downstaging analysis

The combined Nordic trials NCS1&2 (total 620 patients; NAC + cystectomy *vs.* cystectomy alone) showed a hazard ratio of 0.80 (95% confidence interval, 0.64–0.99) P=0.049, for overall survival, in favor of NAC. In the subgroup analyses, there was a statistically significant survival benefit within the T3 group, comparing outcomes of the experimental arm with the controls, HR of 0.69, for overall survival. There was also a similar HR (0.85) in the T2 group, but without statistical significance. At 5 years median observation (all patients, n=620), there was an absolute risk reduction for death (ARR) of 8% in favor of NAC. In the T3-subgroup analysis, there was an ARR of 11% in favor of the experimental NAC arm and in the T2-subgroup analysis, there was an ARR of 7% in favor of the NAC arm (7). Even if the clinical staging in NCS1&2 did not confirm with the suggested definitions of HR resp LR, especially in terms of denoting LVI (which never was analyzed), the subgroup analysis comparing outcomes of T2 and T3, respectively, does give a plausible hint of some suggested differences in survival advantages between the subgroups. In our follow up study from 2012, we also established that complete response to NAC (CR, i.e., pT0N0M0—downstaging of the primary tumor), could be utilized as a surrogate marker for treatment efficacy and for long term survival analysis. Interestingly of the 449 patients evaluated, we had included 92 cT2 patients in the experimental arm and 107 cT2 patients in RC-only control arm and the 5-year survival for the CR-patients of the former group was 86.2% while for the CR-controls only 59.1% (10).This result suggests high interindividual differences and that clinical staging (as well as downstaging-analysis) might not be the most reliable and final tool for decision-making.

The results of the present article

Totally 1,931 patients were identified to be evaluated in the study, including 1,025 classified as LR and 906 as HR, with a median follow-up in alive patients alive, of 6.3 years. 300 patients underwent NAC-treatment, including 104 LR patients. In LR patients, the receiving NAC was associated with significantly increased odds of downstaging to pT0 (OR =3.05; 95% CI, 1.89–4.93; P<0.001) as well as <pT2 (OR =2.53; 95% CI, 1.64–3.89; P<0.001) at RC. Downstaged LR patients experienced significantly improved CSS and OS compared to non-responders (P<0.001). Despite this, CSS and OS did not significantly differ between NAC-LR-patients and NAC-naïve patients, yet—most probably due insufficient statistical power. Further, the investigators observed a 68% 5-year CSS among LR patients who underwent up front RC. The investigators also found that for the NAC-eligible LR patients treated with immediate RC, 14% had an indication for adjuvant chemotherapy but were unable to receive it due to perioperative events—and thus missing their opportunity to receive perioperative cisplatin. The authors conclude: "*These data support continuing to offer NAC to LR patients, and may be useful for counseling patients who are considering foregoing NAC due to concerns over toxicity and/or the perception of modest benefit*."

Aspects on chemotherapy augmentation of antitumoral immunity

In 2017, our group showed that doxorubicin (eqv. to adriamycin—part of MVAC) treatment of B cells resulted in increased expression of CD86 and concordantly increased CD4+ T cell activation Furthermore, doxorubicin caused decreased expression of the anti-inflammatory cytokines IL-10 and TNF-α. Finally, B cells from urinary bladder cancer patients, treated with NAC (containing adriamycin), showed increased CD86-expression, and we concluded that doxorubicin induces CD86 expression on B cells, enhancing their antigen-presenting ability in vitro, which also was verified in the investigated NAC-patients (11). In 2018 we published a translational study in which we prospectively analyzed the effects of NAC on immune cell subsets of 40 patients with MIBC (28 cT2-patients, 10 cT3-patients and only 2 cT4a-patients). We found that NAC had a positive effect on immune effector T cells, whereas an opposite, diminishing effect was observed for immune-suppressive regulatory T cells. We concluded that NAC reinforces

the antitumor immune response in MIBC-patients (12). In another translational study published the same year, we investigated blood, tumor and regional lymph nodes, which were acquired from the study patients at the time of transurethral resection (TUR-b) and intraoperatively during RC. Tumor-infiltrating CD4+ lymphocytes were significantly hypomethylated in all four investigated lineage loci compared to CD4+ lymphocytes in lymph nodes and blood (IFNG, IL13, IL17A and FOXP3). Examination of individual lymph nodes displayed different methylation signatures, suggesting possible correlation with future survival (in terms of downstaging). More advanced post-cystectomy tumor stages (non-responders) correlated significantly with increased methylation at the IFNG-4,229 bp locus. Patients with CR (i.e., pT0N0M0) to NAC displayed significant hypomethylation in CD4+ T cells for all four investigated loci, most prominently in IFNG ($P<0.0001$). NAC seemed to result in a relocation of Th1-committed CD4+ T cells from blood, presumably to the tumor, indicated by shifts in the methylation patterns, whereas no such shifts were seen for lineages corresponding to IL13, IL17A and FOXP3 (13).These translational investigations point at NAC being of great importance for augmentation of antitumoral immunity, most probably on an epigenetical level.

Further the authors, Lyon *et al.* also acknowledge the possibilities of molecular substratification, as recently presented by a multicenter group working in this field with reference specifically to NAC-responses in MIBC (14). Yet in the light of the complexity of tumor heterogeneity, especially in terms of clonal evolution in metastatic deposits (15) and the important need for adding a second corresponding immunological layer (on a patient-individual basis), any taxonomic subclassification requires to be combined with a dynamic and individual immunological profiling for maximizing treatment efficacy. The high likelihood of adequate and potent immune responses being not mainly restricted to the primary tumor, but foremost to the level of tumor draining lymph nodes (12,16), does not simplify the task of defining a robust and individually based immunological profiling.

Individualized medicine needs to pinpoint the immunological status and possible immune-responses in every MIBC-patient subject to the choice; NAC or no-NAC, and the stratification of patients being deemed as responders or non-responders can thus not be based on uncertain cT-staging or even presence or absence of LVI.

Summary

Although the authors can validate the proposed risk stratification originally suggested by Culp *et al.*, they reach to the conclusions that all eligible MIBC-patients should yet actively be offered the suggested option of NAC, regardless if the patients are stratified as LR or HR. We are all aware of the dire needs—early in the process (most probably at time of analysis of the primary TURb-specimens)—to differentiate between responders versus non-responders to NAC. The goal is to proceed with alternative treatment options for the latter group (most probably in combination with up front RC). Yet, in agreement with Lyon *et al.*, the response stratification in LR versus HR is far from enough and not an option in modern oncological urology, especially not in the rapidly evolving era of tumor immunology. The scientific community needs to strive for more reliable and reproducible science on molecular subgrouping, epigenetical response/non-response data and on corresponding tumor-immunological profiling based on individual and specific responses to NAC treatment, before we can proceed to exclude NAC-eligible patients from this successful therapy.

It is not an option for me, as an active clinician in the specific area of MIBC, to motivate my NAC-eligible LR patients (and their families) to actively abstain from a well-researched treatment which might lead to an ARR for death of 7% (5 years median time of observation), compared to less favorable survival projections following immediate RC.

Acknowledgments

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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