

EDITORIAL COMMENT

Don't throw out the baby with the bath water!

Editorial comment to DaBlCa-17: nationwide observational study in Denmark on survival before and after implementation of neoadjuvant chemotherapy prior to cystectomy for muscle-invasive bladder cancer

Amir Sherif

Department of Diagnostics and Intervention, Urology and Andrology, Umeå University, Umeå, Sweden

The authors of the DaBlCa study number 17 [1] are to be commended for their effort to try to elucidate the effects of the guideline recommendation for neoadjuvant chemotherapy (NAC) prior to cystectomy for muscle invasive bladder cancer (MIBC) [2].

In brief, in randomized clinical trials of patients with urothelial MIBC, overall survival (OS) was longer in the experimental arm with NAC versus the control arm with an absolute risk reduction (ARR) of 5%–8% in a median follow-up time of 5 years [3, 4]. These results have been reported in large meta-analyses [5, 6] and have been translated into recommendations in the European Association of Urology (EAU) Guidelines [2].

In this study, the authors took advantage of a natural experiment that occurred in Denmark when the EAU guidelines were changed to include a recommendation for NAC in urothelial MIBC patients. The authors assessed the effect of the recommendation in two analyses.

In the first analysis, the authors compared outcome in periods before and after the recommendation had been published. This analysis was hampered by that only 60% of patients received NAC in the period after the recommendation [7]. In the second analysis patients treated with or without NAC in the latter period were compared. Since there was no randomization, it cannot be ignored that patients with a more aggressive cancer were more prone to receive chemotherapy. My other concern is that the study neither included data on what chemotherapeutic agent that was used nor the number of cycles. Patients who receive one or two cycles are suboptimally treated since at least three cycles are needed and consequently the current debate concerns superiority of four versus three cycles [8–11].

Thus, the authors risk ending up with a subcohort of suboptimally treated (only 1 or 2 cycles) *NAC-to-be-but-NAC-failed-patients* and mixing them with completely NAC-treated patients versus *quick-to-RC-No-NAC-patients*. Patients who have received one or two cycles but not completed all their cycles have usually done so due to adverse events (AEs) [12]. That in itself, adds a selection bias. The added AEs, if serious, in themselves in the subcohort of *NAC-to-be-but-NAC-failed-patients*, might negatively affect long term survival – apart from AE-superimposed *time delays* (as, for example, thromboembolic

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AEs leading to cystectomy delays due to anti-thrombotic treatment before cystectomy). In the study by Eriksson et al., almost 10% of the NAC-patients had thromboembolic AEs (12). What percentage had this time-delaying and also potentially lethal AE in this study population?

Furthermore, it is unknown if patients with clinically diagnosed lymph node metastases (cN+) or very advanced local stage (cT4b) were included in this study. Chemotherapy prior to cystectomy to these patients, is defined as *induction chemotherapy* and not NAC, and hence those categories should not be included in a study of the effects of NAC treatment.

Implementation or rather adherence to a recommendation includes actual treatment of patients. The authors have named the study 'before and after implementation etc'. Thus, implementation of an intention-to-treat-regiment is evaluated. Not the *actual treatment* by all standards, being found in both defining the study population as well as defining the minimum amounts of received NAC cycles.

In order to not study 'an implementation' of an intention-to-treat-regiment, but instead study the treatment itself, the study population needs to be solely restricted to patients staged as cT2a-4aN0M0 *and* that the treatment should be administered according to guidelines and routines of the medical oncologists, meaning that patients with cN+ and/or cT4b and patients who received less than three cycles of NAC need to be excluded from the analysis.

In conclusion, in a population in which slightly more than half of the patients received the recommended treatment, the outcomes were not as good as in randomized control trials (RCTs) in which the treatment was implemented. In my view, these data support the importance of adherence to guideline recommendations if similar results are to be obtained as in RCTs. Furthermore, the study does not contradict the results obtained in controlled RCTs. In other words, don't throw out the baby with the bath water!

Reply to Don't throw out the baby with the bath water!

Stefanie Korsgaard Körner^a and Jørgen Bjerregaard Jensen^b

^aDepartment of Urology, Aarhus University Hospital, Aarhus, Denmark; ^bDepartment of Clinical Medicine, Aarhus University, Aarhus, Denmark

We appreciate the comment from Sherif on our study [1]. As stated in the introduction, neoadjuvant chemotherapy (NAC) with four cycles of gemcitabine-cisplatin was the recommended treatment according to the Danish guidelines since 2013 [13]. The specific regimen and standard number of cycles is therefore stated even though information regarding the number of patients completing all cycles versus patients stopping prematurely is not stated. We aimed to evaluate the potential benefit of introducing NAC in the overall patient population and not to do a sub-analysis of patients completing all cycles with a comparison to less fit patients not completing all cycles as this would be heavily hampered by selection bias. As we compared a cohort after the implementation of NAC to a cohort before the implementation, we could not have excluded patients before introduction of NAC who theoretically would have completed less than three cycles of NAC as these patients were never exposed to NAC. Furthermore, if only selecting patients who completed three or four cycles of NAC and comparing these patients to patients not treated with NAC or with less than three cycles of NAC, this would surely introduce severe selection bias. We have previously described reasons for not receiving NAC in the latter cohort [14]. This information was not available retrospectively in

the pre-NAC cohort as these patients had not been evaluated with regard to potential NAC.

As Sherif correctly states, it cannot be ignored that patients with more aggressive cancer were more prone to receive NAC. However, the methods section clearly states that patients with N+ disease or very advanced local stage (cT4b) were not included in the study since these patients were not treated with NAC. Therefore, patients undergoing downstaging chemotherapy were excluded from both cohorts. Moreover, the fact that selection of patients for NAC versus no NAC could have been influenced by different reasons in the latter cohort is actually the primary reason for our study design where we do not introduce the selection bias as otherwise suggested by Sherif.

We are aware of the limitations to the study design and therefore state in the discussion that reservations should be made for our results versus the true effect of NAC on survival outcomes. On the other hand, we do not find it correct to continue basing present treatment on more than 30-year-old studies on selected study patients. Especially if present real-world evidence suggests that we offer a potentially harmful treatment with no clear benefit for our present patients.

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