Editorial

Neoadjuvant chemotherapy for bladder cancer: Two decades on

Neoadjuvant chemotherapy (NAC) in conjunction with radical cystoprostatectomy has been used over few decades to improve survival in patients with muscle-invasive bladder cancer. Randomized trials on the subject have shown an absolute 10-year overall survival benefit of 5%–8% as opposed to the toxicity of chemotherapy in few.[1,2] A dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) or gemcitabine and cisplatin (GC) are currently recommended regimens with better reported efficacy and tolerance rates than standard MVAC regimen. Six-cycle dose-dense MVAC has recently shown a survival advantage over GC combination as neoadjuvant therapy; however, the concerns of higher toxicity remain compared to GC.[3]

This issue of the journal carries two retrospective studies from tertiary hospitals in India on NAC. Although Jayanth *et al.* report a 5-year overall survival difference of 60 versus 45% in favor of NAC, there are no meaningful numbers remaining at 5 years for such comparison as per the Kaplan–Meier charts. The steep steps of the NAC curve are testimony to fewer events and numbers at risk in this arm. The selection bias is obvious with older cohort receiving no NAC while more recent and healthier cohort with higher glomerular filtration rate (GFR), hemoglobin, and serum albumin levels receiving NAC. Thus, while the study does provide some data in Indian scenario as a step forward, it is difficult to derive meaningful interpretations, particularly when the recurrence-free survival and overall survival seem to be discordant. Both NAC and adjuvant chemotherapy were significant predictors of survival leaving room for pre- or postoperative use of chemotherapy still open. Here, one should remember that while postsurgery adjuvant chemotherapy may sound appealing, in a real-world scenario, 25%–33% of preoperative eligible cases may be left as chemotherapy noneligible due to fall in performance status, perioperative complications, or loss of renal function.[4]

The second paper by Nuthalapati *et al.* deals with perioperative complications. There was no difference in complication rates, type, or severity among patients who had NAC compared to those undergoing cystectomy up-front. However, as noted, NAC was preferred in young and high GFR with nearly 25% unable to complete planned NAC. Logically, one may expect fewer complications in younger cohort, and it remains unclear in this study design if one could attribute equal complications in both the groups to use of NAC in this younger cohort.

Both these studies reflect the real-world scenario in India where adoption of routine NAC for eligible cases is gradually improving but still remains dismal at 20%–25%. Despite high-level evidence available in favor of NAC for nearly two decades, there are many factors which dissuade practitioners from its routine acceptance for all cases. These include the limited incremental benefit with respect to numbers needed to treat ranging from 10-20:1. Further, the toxocity of NAC prevents continuation of NAC in 1 out of 4 cases.[5] Affordability, accessibility, and availability of NAC preclude its acceptance at secondary hospitals Such underutilization of NAC is a worldwide trend and not limited to the Indian subcontinent or Asia.

The median age of cystectomy in the sixth decade in Indian studies, compared to the seventh decade in western literature, is also a point to ponder raising questions such as possible genetic predisposition, higher exposure to smoking, air pollution, or occupational hazards. Consequently, the issue of difference in biology of disease in the Indian subcontinent also becomes important. Even in the setting of non-muscle invasive bladder cancer, studies from indian sub-continent suggest less incidence of carcinoma-in-situ and higher percentage of cases with low grade but T1 disease[6], raising similar concerns of possible differences in disease biology These facts underpin the need to conduct a well-designed randomized trial in Indian setting to decipher the role of NAC. A retrospective study from Japan showed no difference in survivals with or without NAC.[7]

Besides survival advantage, NAC also provides an opportunity to select patients for bladder preservation.[8] The evidence is gradually accumulating in this regard and looks promising as a future perspective for those who have good or complete response to NAC. Additionally, availability of immunotherapy has opened a newer available channel of neoadjuvant therapy in combination with NAC. Early results with nivolumab, pembrolizumab, durvalumab, tislelizumab, and tremelimumab have all shown encouraging results.[9] For those with persistent T2–4 or N+ disease after having received NAC, the use of adjuvant immunotherapy has been shown to improve disease-free survival against a placebo, though overall survival still remains questionable in this setting.[10,11]

Increasing use of NAC also brings into question the use of routine lymphadenectomy with radical cystoprostatectomy. Survival benefit of concomitant bilateral pelvic lymphadenectomy had been questionable. Most previous evidence in favor of lymphadenectomy was retrospective and in an era when NAC utilization was low. NAC works on the principle of killing micrometastasis. Traditionally, lymphadenectomy also served through the same principle of tackling regional nodal metastasis. Recent trials suggest no survival benefit with the use of extended lymphadenectomy[12] versus standard lymphadenectomy, with 57% of trial population having received NAC. It is difficult to interpret if standard lymphadenectomy would provide any survival benefit, with higher utilization of NAC. It would be interesting to know the subgroup analysis comparing survivals among those having received NAC versus no NAC in those undergoing standard lymphadenectomy.

Overall, with more studies on NAC and supportive evidence, one can hope that surgeons use and extend the benefits of NAC to deserving patients.

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