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LETTER TO EDITOR

Advantages and Disadvantages of Neoadjuvant Chemotherapy in Muscle-Invasive Bladder Cancer

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Neoadjuvant chemotherapy (NAC) has been a standard treatment in the management of muscle-invasive bladder cancer (MIBC), especially for cisplatin-eligible patients. However, its widespread adoption is hampered by unresolved controversies. Various systematic reviews and meta-analyses support the role of NAC in improving survival. While in a meta-analysis published by Li G and colleagues in 2017, no difference in Overall Survival (OS) was observed between the group receiving NAC and the group that did not receive NAC (1). In addition to its advantages, it is necessary to examine its possible disadvantages and challenges.

A 2004 Cochrane review, reported a 14% relative reduction in mortality with cisplatin-based NAC (HR 0.86, 95% CI: 0.77–0.95), stating an absolute survival improvement of 5% (1-7%) at five years (2). Considering the lower limit of the confidence interval suggesting an absolute benefit of only 1%, the number needed to treat (NNT) would be 100, implying that NAC would need to be administered to 100 patients for a single individual to have a benefit.

Additional support came from other studies, which found a statistically significant OS benefit for NAC plus radical cystectomy (RC) over RC alone (HR 0.82, 95% CI 0.71–0.95, p=0.009). However, we should be careful when judging how strong these results are. Many studies included in these meta-analyses differ significantly in their design and patient selection. While some studies compare NAC+RC with RC alone, others include radiation therapy or mixed local treatments in the control group. Also, chemotherapy regimens were not the same in different studies in meta-analyses. This mix of treatments makes it harder to trust the combined results. Moreover, most trials are retrospective or observational, raising the risk of selection bias, with only two RCTs addressing survival outcomes. Patients chosen for NAC are often younger, fitter, and have better renal function compared to those undergoing RC alone (3,4). These limitations suggest that the "true" effect size of NAC may be smaller than reported.

Another important concern is the delay in performing surgery for patients. In clinical practice, time is a critical factor for MIBC patients. Neoadjuvant chemotherapy (NAC) regimens typically require 2–3 months, and in non-responders, this delay may permit disease progression. In some cases, patients may become ineligible for surgery during this period due to clinical deterioration or metastasis. This issue is further compounded by the absence of reliable biomarkers to identify likely responders (4).

Drug toxicity presents another challenge. Classical MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) regimens are associated with high rates of severe hematologic adverse events, with grade 3–4 neutropenia occurring in up to 75% of patients. Febrile neutropenia and nausea have also been reported. While newer regimens such as gemcitabine/cisplatin (GC) or accelerated MVAC (AMVAC) may reduce some complications, they still carry hematologic risks. The VESPER trial (2021) reported higher rates of grade ≥3 gastrointestinal toxicities and fatigue in the MVAC group compared to GC (5). Importantly, most studies have focused on short-term side effects of chemotherapy, while long-term consequences, particularly regarding sexual and urinary function, remain underexplored.

Despite over 90% of urologists acknowledging the benefits of neoadjuvant chemotherapy (NAC), concerns about its side effects, potential delays in surgery, and the risk of disease progression result in only about 30% of eligible patients being referred for NAC (6).

Another important issue concerns the potential effects of NAC on pathological staging. Although pathological down-

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staging is often considered a valuable clinical endpoint, its correlation with long-term survival remains uncertain. Several studies have reported that even patients who achieve pT0 following NAC may experience early recurrences, indicating that downstaging alone may not be a reliable prognostic marker. In conclusion, the survival benefit of NAC in MIBC is increasingly supported by clinical evidence. But its routine use should be approached with caution due to persistent methodological and practical limitations. Although some studies have reported statistically significant benefits of NAC, the corresponding hazard ratios were generally low. This raises the concern that, with more robust methodology and appropriate statistical adjustments, such findings might no longer reach statistical significance. Until validated biomarkers and reliable patient selection tools are available, clinicians must carefully balance the modest survival benefit against potential harms. Further high-quality randomized trials are essential to define the appropriate role of NAC in modern bladder cancer management.

Appendix

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Conflict of Interest

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Authors contribution

Farzad Allameh and Seyyed Ali Hojjati contributed equally to the conception, drafting, and revision of this letter. Both authors read and approved the final manuscript.

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