

Refining the use of neoadjuvant chemotherapy in locally advanced bladder cancer: from conviction to optimization

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Radical cystectomy (RC) remains the standard of care as local treatment of muscle-invasive bladder cancer (MIBC). However, the cancer-specific survival is approximately 50%, depending on the presence of extravesical extension and lymph node metastases. In other words, nearly 50% of patients develop metastases within 2 years after RC, implying the presence of micro-metastases at the time of surgery. Neoadjuvant chemotherapy (NAC) has been shown to improve survival of patients and international guidelines recommend NAC based on the available level I evidence (1,2).

From clinical trials to daily practice: an ever-present need for conviction

Despite randomized studies and meta-analyses demonstrating the survival benefit of cisplatin-based combination chemotherapy before RC, practice studies reported in the mid-2000s showed very low implementation of NAC (less than 10%) in daily practice. Potential reasons include patient ineligibility related to renal dysfunction, toxicity of NAC, delay in performing RC, patient preference against chemotherapy, and probably most importantly low propensity of urologists and medical oncologists to use NAC. After many years of practice lagging behind evidence, more recent surveys suggest that the use of NAC has been increasing worldwide during the 2010s (3-6). However, it remains clear that not all patients who are likely to benefit

from NAC receive it, suggesting that continuous efforts are required to convince more urologists and oncologists to use it.

What is the optimal chemotherapy regimen? A need for clarification

Level I evidence regarding the overall survival benefit of NAC was obtained with cisplatin-based regimens that are no longer currently used, such as the 4-week standard MVAC regimen which combines methotrexate, vinblastine, doxorubicin and cisplatin, or the 3-week CMV, which includes the same drugs without doxorubicin (7,8). Since standard MVAC has been supplanted in the metastatic setting by less toxic regimens, namely gemcitabine-cisplatin (GC) and dose-dense MVAC (ddMVAC), efforts are being made to evaluate these regimens in the preoperative setting.

In the June 2018 issue of the *Journal of Urology*, Zargar *et al.* reviewed the medical records of 319 patients with cT3-4aN0M0 MIBC who underwent NAC and RC from 2000 to 2015 in 20 institutions (9). One hundred patients received ddMVAC and 219 were treated with GC. Baseline characteristics were similar between the two groups except for age (patients who received ddMVAC were younger) and the proportion of variant histology features (higher in the ddMVAC group). Overall 90% and 86.3% of patients received 3 or 4 cycles of NAC in the ddMVAC and GC groups, respectively. A significantly lower rate

of pathological complete response rates (ypT0N0) were observed in patients treated with GC (14.6% vs. 28%, $P=0.005$). Similarly, the pathological partial response rates (ypT1N0 or less) was lower (30.1% vs. 41%, $P=0.07$). These results translated in longer overall survival for patients treated with ddMVAC (mean survival of 7 vs. 4.6 years, $P=0.001$). In multivariate analysis, lymph node invasion, hydronephrosis and GC regimen were independently associated with shorter overall survival.

This study suggests that ddMVAC could be the optimal regimen for NAC. As ddMVAC is administered on a shortened 2-week schedule with G-CSF support as compared to classic MVAC, this amounts to doubling the dose-intensity of cisplatin and doxorubicin while reducing by one third the dose-intensity of methotrexate and vinblastine. In metastatic disease, a phase III trial comparing classic MVAC to ddMVAC showed an improvement in complete response rate from 11% to 25% ($P=0.006$) and a significant benefit on overall survival from 13.5% to 22% at 5 years ($P=0.04$) in the ddMAVC arm (10). These findings could result from the doubling of the cisplatin dose intensity and may suggest that an increase in pathological response rate could be achieved with ddMVAC in the neoadjuvant setting. However other single institution, retrospective series reported comparable outcomes of GC and ddMVAC regimens (11,12). Considering the retrospective, nonrandomized design of these studies, we must be guarded in drawing definitive conclusions for daily practice. Clarification to answer this question will be hopefully provided by the results of the recently closed VESPER study conducted by the French Genito-urinary Tumor Group (GETUG). Five hundred patients were randomized to receive chemotherapy for 3 months with either 6 cycles of ddMAVC or 4 cycles of GC in the perioperative setting. The issue of the optimal number of cycles will thus also be assessed.

Which patients benefit from the NAC? The need for accurate biomarkers

The identification of patients most likely to benefit from NAC certainly would help to a better implementation in daily practice. In recent years, progress in genomic characterization of urothelial cancers led to the identification of molecular subtypes (13,14). Although further harmonization in subtype classifications published so far is required for clinical applicability, patients with basal/squamous—like tumors have been reported as best

potential candidates for NAC. In the same time, DNA damage response—associated genes could be of interest in the prediction of response to cisplatin-based NAC. Data collectively suggest better outcome in tumors with deleterious DNA repair mechanisms (15). However clinical validation in prospective trials is required before using these promising approaches in the daily management of patients.

At the end of the beginning

There is still a long way to go to cure the majority of patients with bladder cancer and progress will only be possible with a multidisciplinary approach. The main objectives for the coming years will be to better select patients who may benefit from perioperative medical treatments, to evaluate the efficacy of immunotherapy and its potential role alongside chemotherapy, and to propose an alternative to chemotherapy for patients unfit for cisplatin.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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