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Contemporary best practice in the use of neoadjuvant chemotherapy in muscle-invasive bladder cancer

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Abstract

Background: We aimed to provide a comprehensive literature review on the best practice management of patients with nonmetastatic muscle-invasive bladder cancer (MIBC) using neoadjuvant chemotherapy (NAC).

Method: Between July and September 2018, we conducted a systematic review using MEDLINE and EMBASE electronic bibliographic databases. The search strategy included the following terms: Neoadjuvant Therapy and Urinary Bladder Neoplasms.

Results: There is no benefit of a single-agent platinum-based chemotherapy. Platinum-based NAC is the gold standard therapy and mainly consists of a combination of cisplatin, vinblastine, methotrexate, doxorubicin, gemcitabine or even epirubicin (MVAC). At 5 years, the absolute overall survival benefit of MVAC was 5% and the absolute disease-free survival was improved by 9%. This effect was observed independently of the type of local treatment and did not vary between subgroups of patients. Moreover, a ypT0 stage (complete pathological response) after radical cystectomy was a surrogate marker for improved oncological outcomes. High-density MVAC has been shown to decrease toxicity (with a grade 3–4 toxicity ranging from 0% to 26%) without impacting oncological outcomes. To date, there is no role for carboplatin administration in the neoadjuvant setting in patients that are unfit for cisplatin-based NAC administration. So far, there is no published trial evaluating the role of immunotherapy in a neoadjuvant setting, but many promising studies are ongoing.

Conclusion: There is a strong level of evidence supporting the clinical use of a high-dose-intensity combination of methotrexate, vinblastine, doxorubicin and cisplatin in a neoadjuvant setting. The landscape of MIBC therapies should evolve in the near future with emerging immunotherapies.

Keywords: immunotherapy, muscle-invasive bladder cancer, neoadjuvant chemotherapy (NAC), platinum-based chemotherapy

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Introduction

Bladder cancer (BC) is the fourth most frequent cancer in the United States, with 79,030 new cases and 16,870 deaths estimated for 2017.[1] Radical cystectomy (RC) and extended bilateral pelvic lymphadenectomy are the cornerstone of management for muscle-invasive bladder cancer (MIBC) patients. However, oncological outcomes of RC need improvement, as patients with pT2 and pT3a lymph-node-negative (pN0) tumors harbor a 89% and 78% 5-year recurrence-free survival, respectively. Moreover, the 5-year recurrence-free survival for pT3b tumors is 62% and for pT4 tumors is 50%. Patients with lymph-node involvement harbor even poorer oncological outcomes with a 5-year recurrence-free survival of approximately 35%.[2]

There is an unmet need to enhance therapy dedicated to MIBC patients. In this way, neoadjuvant chemotherapy (NAC) has been widely proposed and evaluated. Even if sufficient data support the benefit associated with its administration, there is still a low agreement within the uro-oncological community for daily practice. In theory, the neoadjuvant setting is ideal; it allows control of micrometastatic disease and its administration remains easier than after a major surgery such as RC due to the loss of renal function after surgery, mainly. Delaying the surgery and the inability to predict unresponsive tumors (thus selecting the best candidates to chemotherapy) are the main drawbacks of this therapeutic strategy, explaining the low uptake worldwide. Many regimens have been tested over the years and nowadays both American Urological Association and European Association of Urology guidelines advocate for a platinum-based chemotherapy regimen in the neoadjuvant setting.[3,4]

In this manuscript, we aimed to provide a comprehensive literature review on the best practice management of patients with nonmetastatic muscle-invasive bladder cancer (NMIBC) using neoadjuvant chemotherapy (NAC).

Methods

Between July and September 2018, we conducted a systematic review using MEDLINE and EMBASE electronic bibliographic databases. The search strategy included the following terms: Neoadjuvant Therapy and Urinary Bladder Neoplasms. The terms were combined with the Cochrane MEDLINE filter for controlled trials of interventions. Only studies written in English were included. The searches were rerun just before the final analyses and no further studies were retrieved for inclusion. We included only prospective randomized trials and meta-analyses. In case prospective randomized trials were not available, retrospective studies were thus included. Titles with or without abstracts of studies retrieved using the search strategy and those from additional sources were screened independently by two review authors to identify studies that potentially met the inclusion criteria outlined above. The full texts of these potentially eligible studies were retrieved and independently assessed for eligibility by two review team members. Any disagreements between them over the eligibility of particular studies were resolved through discussion with a third reviewer. Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.

Rationale for neoadjuvant chemotherapy for bladder cancer

First of all, NAC and perioperative chemotherapy are two separate entities. The neoadjuvant term is used when the strategy planned is to give a treatment prior to a surgery whereas perioperative or induction is a chemotherapy regimen given to a patient with metastatic or unresectable tumor at the diagnosis (cN+, cM+) that eventually will respond to this systemic treatment and therefore could benefit from a surgical therapy after partial or complete response. In this review, we focused on the outcomes of NAC.

On one hand, chemotherapy administered in a neoadjuvant setting comes with some advantages: the ability to deliver effective systemic therapy while the burden of micrometastatic disease is low; its administration before major surgery theoretically permits improved drug delivery into the bladder, surrounding lymphatic vessels and lymph nodes, and is given in a setting in which the patient's performance status is optimal (patient more fit, no loss of renal function, eligibility to optimal cisplatin-based chemotherapy regimens). Patient's performance status is widely recognized as an important prognostic factor in assessing response to chemotherapy for MIBC patients.[5] Response to chemotherapy is also a well-known prognostic indicator before surgery.

On the other hand, the disadvantages of such therapy have led to controversies explaining the relatively low uptake worldwide for the therapy. Some of the reasons for low adherence to the guidelines are: ignorance or low belief of the evidence supporting NAC for MIBC; delay in surgery, especially in patients that will not respond (old cut-off of the 12 weeks from the time of diagnosis to RC);[6,7] an increased difficulty of the surgical procedure that could lead to increase perioperative morbidity. Regarding the last reason, several recent studies showed no difference in perioperative morbidity or 30–90-day readmission rates in patients treated with NAC prior to RC.[8,9]

Several types of NAC regimens for MIBC have been evaluated over the years. First of all, some trials have proposed a single agent for NAC. These prospective studies showed no benefit of a

single-agent platinum-based chemotherapy[10,11] and a pooled-data meta-analysis using individual patient data confirmed the lack of benefit of such regimens [hazard ratio (HR) = 1.15; p = 0.264].[12] Therefore, investigators used platinum-based multiagent regimens in the next generation of prospective trials. Unfortunately, all of them have in common a relatively low accrual and thus low sample size of patients, not allowing for enough statistical power to demonstrate a benefit of the combined approach (NAC + surgery) over surgery upfront[13–17] (and one unpublished trial by Cortesi *et al*. presented only as an abstract). However, the Advanced Bladder Cancer Meta-analysis Collaboration group combined the results of all of these trials in a meta-analysis.[12] In this meta-analysis, platinum-based regimens significantly improved overall survival [combined HR = 0.86; 95% confidence interval (CI) 0.77–0.95; p = 0.003]. Moreover, the risk of death decreased by 13%. At 5 years, the absolute benefit was 5% and the absolute disease-free survival improved by 9%. This effect was observed independently of the type of local treatment and did not vary between subgroups of patients. Moreover, a ypT0 stage after RC was a surrogate marker for improved oncological outcomes.[18–20]

Chemotherapy type

Platinum-based NAC mainly consists of a combination of cisplatin, vinblastine, methotrexate, doxorubicin, gemcitabine or even epirubicin. Many combinations of dose, number of cycles and types of drugs have been investigated. To our knowledge, the first to describe the MVAC regimen (methotrexate, vinblastine, doxorubicin and cisplatin) were Sternberg *et al*. in 1985.[21] At that time, this therapy was exclusively used in metastatic BC. This therapy is known to be associated with a significant toxicity and requires at least 3 months to complete four cycles. In order to reduce the toxicity of this 'traditional' MVAC therapy, Sternberg and colleagues later described a variation called high-dose-intensity MVAC chemotherapy (HD-MVAC) (known also as dose-dense MVAC or accelerated MVAC).[22] The results showed improvement in response rates, progression-free survival, and overall survival (OS) with HD-MVAC, while inducing lower rates of neutropenia, neutropenic fever, and mucositis. In the neoadjuvant setting in particular, HD-MVAC provides another advantage over standard MVAC because three cycles can be completed within 6 weeks, thus minimizing the interval between diagnosis and surgery. Therefore, HD-MVAC has become over the years one of the standards for NAC. Most of the studies have shown decreased toxicity with a grade 3–4 toxicity ranging from 0% to 26% without impacting oncological outcomes.[23–27] In these studies, about half of the patients achieved either pathological complete response or a downstaging to NMIBC (partial pathological response). Interestingly, 82% of patients with cN1 disease before cystectomy were pN0 at final pathology following HD-MVAC.[24] However, these results need to be interpreted with caution due to the overall low performance of imaging prior to surgery.[28]

HD-MVAC is not the only regimen studied; gemcitabine and cisplatin combination (GC) is an alternative.[29–35] However, there are no prospective, randomized comparisons between GC and MVAC in the neoadjuvant setting. The rationale of GC use is based on one prospective randomized phase III trial including locally advanced (T4b, N2, N3) or metastatic MIBC comparing GC with MVAC.[29] This study showed non-inferior oncological outcomes but a safer toxicity profile in favor of GC. The largest multicenter retrospective series included 212 patients and showed similarly, no significant difference in oncological outcomes but less grade 3–4 toxicity in favor of GC.[30] Recently, Zargar and colleagues reported that HD-MVAC was associated with higher complete pathological response and improved survival rates compared with GC in patients with cT3-4aN0M0 BC treated with RC.[36] These results highlighted the need for more prospective data comparing HD-MVAC and GC.

Regarding the toxicity of chemotherapies, in the initial study of GC *versus* MVAC (metastatic setting of BC), von der Maase and colleagues reported that the toxic death rate was 1% on the GC arm and 3% on the MVAC arm.[37] More GC than MVAC patients had grade 3/4 anemia (27% *versus* 18%, respectively), and thrombocytopenia (57% *versus* 21%, respectively) in this study. Moreover, on both arms, the red blood cell (RBC) transfusion rate was 13 of 100 cycles and grade 3/4 hemorrhage or hematuria was 2%; the platelet transfusion rate was four patients per 100 cycles and two patients per 100 cycles on GC and MVAC, respectively. Additionally, more MVAC patients, compared with GC patients, had grade 3/4 neutropenia (82% *versus* 71%, respectively), neutropenic fever (14% *versus* 2%, respectively), neutropenic sepsis

(12% *versus* 1%, respectively), grade 3/4 mucositis (22% *versus* 1%, respectively) and alopecia (55% *versus* 11%, respectively). Interestingly, quality of life was maintained during treatment on both arms; however, more patients on GC fared better regarding weight, performance status, and fatigue. MVAC is probably associated with greater toxicity compared with GC.

Globally, cisplatin-based regimens are not impacting perioperative outcomes.[8,9,38] Literature is lacking of sufficient evidence to draw conclusion on the effect of GC *versus* MVAC *versus* HD-MVAC on perioperative outcomes.

Although most trial evidence has come from trials evaluating methotrexate, vinblastine, and cisplatin and MVAC regimens, gemcitabine–cisplatin has effectively become the standard neoadjuvant regimen, in part owing to its favorable toxic-effect profile and trial results that have shown comparable metastatic disease results for gemcitabine–cisplatin and MVAC. A recent high-volume center reported an impressive 61% GC use rate of all NAC patients and a low 14% rate of HD-MVAC use ($n = 1113$ patients). Interestingly, they also reported complete response (ypT0N0) rates of 41.3% for HD-MVAC and 24.5% for GC ($p < 0.001$).

Overall, the data above support a neoadjuvant HD-MVAC use prior to cystectomy for T2-T4a N0M0. Hopefully, many studies have reported an improvement in the use of NAC, and the low uptake worldwide seems to decrease over time but still remains too low.[39–44] The results of the last meta-analysis published confirmed the superiority of NAC and showed an 8% absolute improvement in survival at 5 years with a number needed to treat of 12.5.[45]

Regarding our experience and literature data, the optimal course of NAC is HD-MVAC with the following schedule: methotrexate 30 mg/m^2 on day 1; vinblastine 3 mg/m^2 on day 2; doxorubicin 30 mg/m^2 on day 2; cisplatin 70 mg/m^2 on day 2; and pegfilgrastim [granulocyte-colony-stimulating factor (G-CSF) factor] 6 mg on day 3.[26] This cycle is repeated every 14 days until four to six cycles is achieved.

Timing and delay cystectomy

One of the main reasons for low uptake of NAC is risk of increasing the timing between diagnosis of MIBC and surgical treatment (i.e. RC). In fact, a delay between diagnosis and surgery has been shown to negatively impact oncological outcomes. This statement was based on a meta-analysis pooling 12 retrospective and 1 prospective trials.[46] In this meta-analysis, the pooled studies failed to show a linear relationship between delay and prognosis, but the majority confirmed that a longer delay was associated with worse outcomes. They also suggested a window of opportunity of less than 12 weeks from diagnosis of invasive disease to RC. To date, there are no prospective randomized control trials regarding this topic. A recent trial by the Netherlands Cancer Registry with a high number of patients did not show any difference in clinical outcomes: delayed RC (more than 3 months) was not associated with decreased OS adjusting for confounding variables (HR = 1.16; 95% CI: 0.91–1.48; $p = 0.25$).[47] The current research focuses on finding biomarkers reliable enough to predict chemotherapy response. The aim would be ideally to select the patients that could benefit the most from the treatment (i.e. good responders) and in the meantime avoid the administration of an inefficient treatment in those that would not benefit (nonresponders) while not delaying the surgery. In line with this goal some authors have proposed a decision tree.[48]

Patients unfit for cisplatin-based chemotherapy

A consensus definition of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy was released in 2011 among BC experts.[49,50] Patients 'unfit' for cisplatin chemotherapy present at least one of the following criteria: performance status > 1; glomerular filtration rate < 60 ml/min; grade > 2 audiometric loss; peripheral neuropathy; and New York Heart Association (NYHA) class III heart failure. The probability of ineligibility to cisplatin increases with age. By the Cockroft–Gault equation for measurement of renal function, more than 40% of patients with an age over 70 years are ineligible.[51]

Cisplatin can be replaced by carboplatin in other tumors but to date, there are insufficient data to recommend carboplatin-based regimens for NAC. Some randomized trials about metastatic BC have shown that carboplatin-based therapy is inferior compared with cisplatin in this setting with regards to complete response rates and OS.[52–54] So, some authors have also proposed a reduced dose of cisplatin (50 mg/m^2 compared

with the conventional dosing of 70 mg/m^2)[55]; a sequential ifosfamide, doxorubicin, and gemcitabine followed by reduced-dose cisplatin, gemcitabine, and ifosfamide resulted in similar oncological outcomes (pathological downstaging to pT1N0 disease or lower occurring in 50% of patients who underwent RC).

To date, there is no role for carboplatin administration in patients that are unfit for cisplatin-based NAC.[3,4] Standard of care remains upfront RC, but these patients have a high risk of systemic relapse. Therefore, clinical trials for these patients are needed.

Immune-checkpoint inhibitors may be the response for these 'unfit' patients. In 2018, we now have five programmed cell-death 1/programmed cell-death ligand 1 antibody US Food-and-Drug-Administration-approved therapies for urothelial cancer: pembrolizumab, atezolizumab, nivolumab, durvalumab, and avelumab.

The KEYNOTE 045 trial demonstrated a 27% reduction in mortality in favor of pembrolizumab compared with second-line chemotherapy (HR = 0.73; 95% CI: 0.59–0.91). In this study, investigators had the choice of second-line chemotherapy between paclitaxel, docetaxel, or vinflunine.[56] Immunotherapy was also compared with first-line chemotherapy for locally advance MIBC or metastatic bladder cancer in this 'unfit' population.[57] In this study, atezolizumab resulted in a 23% objective response rate per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and a 9% complete response rate.[58]

So far, there is no published trial interrogating the role of immunotherapy in a neoadjuvant setting but many promising studies are ongoing (i.e. ABACUS, PURE-01, PANDORE). The landscape of available drugs for BC may dramatically change in coming years.

Patient evaluation during chemotherapy cycles

As we discussed earlier, identifying NAC responders is challenging, and enhancing the detection of those responders may be the key for a broader acceptance of NAC. There are little available data suggesting the use of one imaging modality after two chemotherapy cycles.[59–61] Computed tomography (CT), magnetic resonance imaging and positron-emission tomography CT have shown a relatively low ability to predict NAC response so far. More studies are needed to assess imaging modality reliability.

Molecular tumor profiling in transurethral resection of bladder tumor specimens might also be a useful tool. Tanaka and colleagues recently described a prediction score on the basis of expression profiles of 14 predictive genes.[62,63] The authors validated the clinical significance of the system, by applying 22 additional cases of BC patients and found that the scoring system correctly predicted clinical response for 19 of the 22 test cases.

Seiler and colleagues performed a whole transcriptome profiling on pre-NAC transurethral resection specimens from 343 patients with MIBC.[64] They used a single-sample genomic subtyping classifier to predict four consensus molecular subtypes (claudin low, basal, luminal infiltrated and luminal) with good accuracy (73%). Luminal tumors had the best OS with and without NAC. Claudin-low tumors were associated with poor OS, irrespective of treatment regimen. Basal tumors showed the most improvement in OS with NAC compared with surgery alone. Their results suggest that patients with basal tumors should be prioritized for NAC. Of course, more studies are needed but unanswered questions about NAC should be assessed in coming years.

Conclusion

There is a strong level of evidence supporting the clinical use of a HD combination of methotrexate, vinblastine, doxorubicin and cisplatin in a neoadjuvant setting. Old controversies about NAC may already have been answered. The landscape of MIBC therapies should evolve in the near future with emerging immunotherapies.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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