Editorial

# Perioperative chemotherapy for muscle-invasive bladder cancer: the importance of multidisciplinary management for evidence-based practice and transformative research

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Perioperative chemotherapy plays a very important role in the management of muscle-invasive bladder cancer (MIBC). Level I evidence from several large randomized clinical trials and a large meta-analysis support the use of cisplatin-based neoadjuvant chemotherapy (NAC) in this patient population (1). Updated results of this meta-analysis published in 2005 included 11 randomized trials and over 3,000 patients and showed a 5% absolute improvement in overall survival (OS) and 9% absolute improvement in disease-free survival at 5 years in patients who received cisplatin-based NAC and local therapy relative to local therapy alone (2). Several large randomized clinical trials of cisplatin-based NAC formed the basis of this meta-analysis including neoadjuvant MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) and CMV (cisplatin, methotrexate vinblastine) (3,4). However, data supporting the use of adjuvant chemotherapy in this patient population have not been as robust. Several randomized trials that compared immediate *vs.* delayed cisplatin-based chemotherapy in patients with high risk pathologic features at the time of cystectomy (pT3/T4, N+), including the EORTC 30994 trial, were underpowered due to poor accrual and consequently none of these trials showed an OS benefit with adjuvant therapy (5). A large meta-analysis that included 9 adjuvant trials and a total of 945 patients did show OS advantage with adjuvant treatment (pooled HR =0.77; 95% CI, 0.59–0.99; P=0.049) (6), however, concerns have been raised regarding variability in patient and treatment characteristics as well as in endpoint definitions among the trials included in the meta-analysis. Benefit of adjuvant chemotherapy in pT3/T4 and/or N+ bladder cancer was additionally supported by a large retrospective population-based observational study suggesting an improvement in OS for patients who received adjuvant chemotherapy as opposed to observation after radical cystectomy (HR =0.70; 95% CI, 0.64–0.76) (7). Although certainly suggestive of OS benefit with adjuvant chemotherapy in patients who had not received NAC, the data do not amount to level I evidence from randomized controlled trials.

The currently accepted standard of care is that patients with MIBC who are cisplatin-eligible as well as eligible for a surgical approach should receive cisplatin-based NAC or enroll into a clinical trial prior to radical cystectomy. Cisplatin-ineligible patients either proceed directly to radical cystectomy or can enroll into a clinical trial. Bladder preservation with concurrent chemo-radiation or clinical trial is another reasonable option for selected patients with certain clinical features. Patients who have high-risk

pathologic stage at cystectomy (pT3/T4 and/or pN+) and had not previously received cisplatin-based NAC should consider cisplatin-based adjuvant treatment with careful discussion of benefits *vs.* risks, while a clinical trial, such as with immune checkpoint inhibitor, is a very reasonable option in this setting for those who either refuse or cannot tolerate cisplatin-based therapy.

In both the neoadjuvant and adjuvant settings in bladder cancer, only cisplatin-based chemotherapy is associated with clinical benefit, whereas the use of carboplatin-based regimens is not consistent with currently-established standard of care. However many bladder cancer patients in either setting remain cisplatin-ineligible per the previously defined criteria (8). This is likely what drives continued use of carboplatin-based regimens by many providers in this setting. The percentage of bladder cancer patients who are cisplatin-ineligible in the perioperative setting due to having impaired renal function is estimated to be as high as 40–50% (9). Other factors, including impaired performance status (ECOG >1), heart failure (NYHA class ≥III), grade ≥2 hearing loss and grade ≥2 neuropathy, may further narrow the potential pool of patients eligible for cisplatin-based treatment. Due to these characteristics in conjunction with logistical factors, lack of data awareness, and fear of toxicity and potential delay in definitive radical cystectomy, the percentage of patients with MIBC who have been treated with perioperative chemotherapy have historically been low. Although it is often difficult to capture all MIBC patients eligible for NAC when extracting data from large databases, studies published in the beginning of this decade suggested the percentage of patients receiving NAC to be around 20% (10,11).

More recently, new data has emerged from both United States and the Netherlands, suggesting that the utilization of perioperative chemotherapy is increasing (12,13). The article by Booth *et al.* discussed in this editorial (14) describes the trend of increased uptake of NAC in the province of Ontario, Canada and investigates other associated trends. This report is an update on prior work from the same group that described practice patterns in Ontario from 1994 to 2008 (15). These prior findings showed NAC utilization in Ontario to be low and not have increased during the studied period despite the availability of emerging data supporting the use of NAC. The current report extends the data on neoadjuvant and adjuvant chemotherapy utilization out to 2013 and reports referral rates to medical oncologists during this time. The picture that emerges is that during the time period under consideration the percentage of patients seen by a medical oncologist prior to cystectomy increased from 12% in 1994–1998 to 32% in 2009–2013. The percentage of referred patients who were treated with NAC also increased from 32% in 1994–1998 to 54% in 2009–2013. The study authors argue that these trends contributed to the overall increase in NAC utilization rates from 5% in 1994–1998 to 19% in 2009–2013 with most of the increase seen at the end of this time period. During the same period adjuvant chemotherapy utilization rates increased only slightly from 15% in 1994–1998 to 20% in 2009–2013. Overall, the utilization rates of perioperative chemotherapy including both neoadjuvant and adjuvant, increased from 19% in 1994–1998 (mostly adjuvant) to 35% in 2009–2013 (about evenly split between adjuvant and neoadjuvant). The study additionally highlights ongoing regional variation of chemotherapy utilization in the province which requires further study. It is also worth pointing out that younger patients and those treated by a surgeon with high clinical volumes were more likely to receive NAC.

Overall, despite the noted increase in both NAC and overall perioperative chemotherapy utilization in MIBC, the rates remain low. Less than half of all patients receive chemotherapy which may be life prolonging. Many patients additionally continue to get carboplatin-based therapy which is not supported by prospective data in this perioperative treatment setting. Thus, although the study certainly highlights progress, it also clearly points out that there remains significant room for continued improvement.

Assigning causality to the trends in increased NAC and perioperative chemotherapy utilization in MIBC patients as discussed in this manuscript is not straightforward. This relates to the inherent limitations in the methodology of this retrospective analysis. A number of other limitations were also apparent in this study. For instance, as rightly pointed out by the authors, the study design did not capture all the cases with clinical T2 stage which would have been candidates for NAC. Consequently, due to the number of NAC-eligible patients in Ontario being underestimated in this study, the true percentage of NAC utilization rate may have been overestimated. It is hard to assess the magnitude of this potential difference. However, it is important to point out that a potential overestimation of NAC utilization would likely have affected the overall estimate of patients receiving NAC in each time period. As the overestimation would likely be consistent across the entire study period there is no reason to doubt the central conclusion of this report showing increase of perioperative

 

chemotherapy in MIBC over time. This limitation would have been addressed if authors had access to individual patient data points, which of course was not feasible in this large database-driven study. The data presented here was additionally limited to patients in Ontario, Canada, and would be difficult to extrapolate to other countries, even countries with similar populations and systems of healthcare delivery. There is a potential advantage to this study being conducted in a healthcare delivery environment where a single-payer system may provide more uniform access to the best recommended treatments. However, even in this setting, the study noted variability in chemotherapy utilization based on region and patients' socioeconomic status, which is likely to occur in many countries.

Despite these limitations, this analysis provides very important population-based data highlighting evolution of treatment trends in MIBC. It describes both how the emergence of new data results in a change in treatment patterns and highlights that significant progress still remains to be made. As the authors suggest, the availability of this and similar datasets can generate additional discussion and may itself drive further improvements in the uptake of these treatments. This hypothesis is of course difficult to test. However, it would seem that data which highlights the simultaneous increase in medical oncology referrals for MIBC patients prior to radical cystectomy and increase in NAC utilization rates during the same period would encourage and facilitate multidisciplinary approaches to patient care. As the paper highlights, in Ontario as in many other locations, there has been increased emphasis on multidisciplinary case conferences. Such approaches generally encourage higher-quality care through facilitating patient timely access to more specialists skilled in the treatment of this challenging disease. They can also help address some of the regional differences that were apparent in this study. It is important to identify barriers for those referrals, which can be both provider and patient related, and nurture an environment of communication and multidisciplinary care for MIBC (16). Provider biases may include fear of losing a patient and/or of delaying definitive local curative therapy, lack of data awareness, and personal anecdotal experience, while patient related factors include low health literacy, low socioeconomic status, lack of support/insurance coverage, long distance and transportation challenges, which can be a hurdle to access to multidisciplinary care for MIBC.

We strongly support the notion that all patients suspected of having MIBC should have a consultation with a medical oncologist to discuss their case. As this study suggests, an increase in these referrals likely contributes to the uptake of treatment approaches that are supported by level I evidence and recommended by treatment guidelines. Additionally, consultation with a medical oncologist can clearly facilitate access to additional treatment options for MIBC, such as novel neoadjuvant therapy clinical trials for both cisplatin-eligible and cisplatin-ineligible patients. The rapidly changing treatment landscape in advanced bladder cancer with the recent advent of immune checkpoint inhibitors appears to be impacting the design of trials in the perioperative setting, with early promising findings in terms of efficacy and tolerability (17). Considering that these agents are better tolerated compared to cytotoxic chemotherapy, timely and successful conduction of those trials is critical. However, the use of immune checkpoint inhibitors remains investigational in the perioperative MIBC treatment setting for the time being. Dynamic interdisciplinary collaboration and continued education of both patients and providers are key for the optimal management of MIBC patients and can also help move the field forward via innovative research. This publication of population-based data by Booth *et al.* is a very important step in continuing this conversation and we should all attempt to keep up the established momentum and stimulate further discussions.

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## Footnote

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

## References

1. Advanced Bladder Cancer Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. Lancet 2003;361:1927-34.
2. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. Eur Urol 2005;48:202-5; discussion 205-6.
3. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant

 

chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 2003;349:859-66.
4. International Collaboration of Trialists, Medical Research Council Advanced Bladder Cancer Working Party (now the National Cancer Research Institute Bladder Cancer Clinical Studies Group), European Organisation for Research and Treatment of Cancer Genito-Urinary Tract Cancer Group, et al. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. J Clin Oncol 2011;29:2171-7.
5. Sternberg CN, Skoneczna I, Kerst JM, et al. Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open-label, randomised phase 3 trial. Lancet Oncol 2015;16:76-86.
6. Leow JJ, Martin-Doyle W, Rajagopal PS, et al. Adjuvant chemotherapy for invasive bladder cancer: a 2013 updated systematic review and meta-analysis of randomized trials. Eur Urol 2014;66:42-54.
7. Galsky MD, Stensland KD, Moshier E, et al. Effectiveness of Adjuvant Chemotherapy for Locally Advanced Bladder Cancer. J Clin Oncol 2016;34:825-32.
8. Galsky MD, Hahn NM, Rosenberg J, et al. A consensus definition of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy. Lancet Oncol 2011;12:211-4.
9. Dash A, Galsky MD, Vickers AJ, et al. Impact of renal impairment on eligibility for adjuvant cisplatin-based chemotherapy in patients with urothelial carcinoma of the bladder. Cancer 2006;107:506-13.
10. Raj GV, Karavadia S, Schlomer B, et al. Contemporary use of perioperative cisplatin-based chemotherapy in patients with muscle-invasive bladder cancer. Cancer 2011;117:276-82.
11. Fedeli U, Fedewa SA, Ward EM. Treatment of muscle invasive bladder cancer: evidence from the National Cancer Database, 2003 to 2007. J Urol 2011;185:72-8.
12. Reardon ZD, Patel SG, Zaid HB, et al. Trends in the use of perioperative chemotherapy for localized and locally advanced muscle-invasive bladder cancer: a sign of changing tides. Eur Urol 2015;67:165-170.
13. Hermans TJ, Fransen van de Putte EE, Horenblas S, et al. Perioperative treatment and radical cystectomy for bladder cancer--a population based trend analysis of 10,338 patients in the Netherlands. Eur J Cancer 2016;54:18-26.
14. Booth CM, Karim S, Brennan K, et al. Perioperative chemotherapy for bladder cancer in the general population: Are practice patterns finally changing? Urol Oncol 2018;36:89.e13-89.e20.
15. Booth CM, Siemens DR, Li G, et al. Perioperative chemotherapy for muscle-invasive bladder cancer: A population-based outcomes study. Cancer 2014;120:1630-8.
16. Almassi N, Glass KE, Lonzer JL, et al. Identifying institutional causes of delay to radical cystectomy among patients with high-risk bladder cancer managed at a tertiary referral center using process map analysis. Urol Pract 2017. [In press].
17. Necchi A, Briganti A, Raggi D, et al. PD11-11 Interim results from pure-01: a phase 2, open-label study of neoadjuvant pembrolizumab (pembro) before radical cystectomy for muscle-invasive urothelial bladder carcinoma (MIUC). J Urol 2018;199:e238.

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