Review Article

Peri-operative chemotherapy for muscle-invasive bladder cancer: status-quo in 2017

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Abstract: The role of perioperative chemotherapy associated with radical cystectomy (RC) for muscle-invasive bladder cancer has been analyzed in several landmark randomized controlled trials (RCTs) over the past decades. With regard to neoadjuvant chemotherapy (NAC), a meta-analysis of level 1 evidence and long-term results from the largest RCTs support its use, which is currently advocated as the standard of care by most of the clinical guidelines worldwide. However, with regard to the delivery of adjuvant chemotherapy (AC), evidence is more contentious. Specifically, several meta-analyses demonstrated a survival benefit associated with the use of cisplatin-based regimen but investigators identified multiple methodological limitations in most of included RCTs. Nonetheless, AC is currently considered for fit patients with adverse pathological features at RC. It is noteworthy that the delivery of such cytotoxic treatment after surgery may maintain significant anti-tumor activity even in those patients who previously received NAC. Finally, given its greater response rate, the methotrexate, vinblastine, adriamycin plus cisplatin combination remains preferentially considered in the neoadjuvant setting, while the gemcitabine plus cisplatin combination is more commonly delivered in the adjuvant setting because of its better toxicity profile. However, no prospective evidence comparing efficacy of both regimens for NAC or AC is currently available.

Keywords: Urinary bladder neoplasms; cystectomy; drug therapy; neoadjuvant therapy; chemotherapy, adjuvant; cisplatin

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Introduction

With more than 79,000 new cases and a projection of 16,390 deaths in 2017 in the US (1), bladder cancer is one of the deadliest cancers worldwide. The standard of care for muscle-invasive disease remains radical cystectomy (RC) with pelvic lymph node dissection (PLND), when there is no evidence of metastatic dissemination at initial diagnosis (2). Nonetheless, the 5-year overall survival (OS) rate after such procedure does not exceed 50–60% in expert centers, given that a significant proportion of these patients will ultimately develop fatal recurrences likely due to the presence of occult

micrometastases at the time of surgery (3,4).

Striving to improve this paradigm, the efficacy of perioperative chemotherapy has been investigated in multiple landmark randomized controlled trials (RCTs) over the past decades (5,6). Interestingly, although treatment strategies involving the use of either neoadjuvant (NAC) or adjuvant chemotherapy (AC) present substantial limitations, there is a clinical rational for both. Indeed, several meta-analyses support the systematic delivery of NAC for all muscle-invasive bladder cancer (MIBC) patients (7) as well as the selective delivery of AC only in those with adverse pathologic features at RC (8,9). Against this backdrop, the present review aims to summarize the available evidence supporting the use of perioperative chemotherapy associated with RC for localized MIBC to provide a 2017 status-quo.

NAC

Rational

As opposed to AC, the delivery of NAC offers several potential advantages for the management of localized MIBC. First, it is well-established that the better preoperative general condition and renal function of RC patients facilitate the infusion of full-dose cisplatin-based regimens. Second, response to NAC at the time of surgery allows to assess chemosensitivity of the primary tumor. Logically, individuals experiencing downstaging of intravesical disease have a better prognosis than nonresponders (10). In addition, complete pathologic response at RC has been shown to correlate with increased OS in a recent meta-analysis by Petrelli *et al.* (10). Based on such rational and the proven efficacy of platinum-based regimens for metastatic bladder cancer (11), several landmark RCTs have explored the role of NAC before RC for localized MIBC.

Efficacy

Historical RCTs and meta-analyses

Oncological outcomes from historical RCTs evaluating the role of NAC are heterogeneous. In 1999, the International Collaboration of Trialists published the first large-scale study including 976 patients with cT2-T4N0 bladder cancer to receive either 3 cycles of NAC (cisplatin, methotrexate and vinblastine) (n=491) followed by local treatment or upfront local treatment (n=485) at 106 participating institutions. Despite a benefit in terms of pathological downstaging with the use of NAC, there was no significant difference in OS between the two treatment groups (HR =0.85; 95% CI, 0.71–1.02; P=0.075) after a median follow-up of 4 years (12). The absolute difference in 3-year OS was 5.5% (95% CI, –0.5% to 11%), with corresponding rates of 55.5% in patients who received NAC and 50% in patients who received upfront local treatment. In addition, there was no significant benefit in terms of locoregional disease-free survival (DFS) with the use of NAC (HR =0.87; 95% CI, 0.73–1.02; P=0.087). Nonetheless, the investigators found a significant difference between the two treatments groups with regard to metastasis-free survival (MFS) favoring the use of NAC (HR =0.79; 95% CI, 0.66–0.93; P=0.007); this translated into an absolute difference of 8% (95% CI, 2–14%) in 3-year MFS, with corresponding rates of 53% in the NAC group and 45% in the upfront local treatment group.

Given that other reports showed contradictory results (13,14), the Advanced Bladder Cancer group from the Cochrane collaboration performed a first individual patient data meta-analysis of available RCTs in 2003 (15). After including 2,688 patients from 10 studies, the investigators found that the use of platinum-based NAC was associated with a 13% OS benefit as compared to local treatment alone (HR =0.87; 95% CI, 0.78–0.98; P=0.016); this translated into a 5% absolute benefit (50% *vs.* 45%, respectively) in 5-year OS. In addition, the use of platinum-based NAC improved significantly DFS (P<0.001) and locoregional DFS (P=0.012) as well as MFS (P=0.001).

However, this first meta-analysis did not include the second largest RCT from the Southwest Oncology Group. Indeed, in 2003, Grossman *et al.* published the results from a study that randomized 317 patients with cT2-T4a bladder cancer to receive either three cycles of methotrexate, vinblastine, adriamycin and cisplatin (MVAC) followed by RC (n=153) or RC alone (n=154) (3). Interestingly, although patients who received NAC demonstrated higher complete pathologic response rates (38% *vs.* 15%; P<0.001), there was only a trend toward adverse OS in patients treated with RC alone (HR =1.33; 95% CI, 1.00–1.76). Specifically, the corresponding 5-year rates of OS were 57% in the NAC group and 43% in the RC alone group (P=0.06). Nonetheless, the risk of cancer-specific death was greater in the RC alone group (HR =1.66; 95% CI, 1.22–2.45; P=0.002).

In this context, a second meta-analysis including 3,005 patients from 11 RCTs has been performed by the Advanced Bladder Cancer group from the Cochrane collaboration in 2005 (7). This updated analysis confirmed the OS benefit of platinum-based NAC as compared to local treatment alone

(HR =0.86; 95% CI, 0.77–0.95; P=0.003) with an absolute improvement of 5% in 5-year OS. In addition, there was a significant DFS benefit with the use of platinum-based NAC (HR =0.78; 95% CI, 0.71–0.86; P<0.001), with an absolute improvement of 9% in 5-year DFS.

Concomitantly, Winquist *et al.* conducted a meta-analysis of summary data from 16 RCTs that included 3,315 patients (16). Of these studies, 11 investigators provided data suitable for OS analysis (2,605 patients). The pooled HR was 0.90 (95% CI, 0.82–0.99; P=0.02) overall but, when restricting the analyses to the 8 RCTs including only individuals who received cisplatin-based NAC, the pooled HR was 0.87 (95% CI, 0.78–0.96; P=0.006); this translated into an absolute benefit of 6.5% in 5-year OS with the use of NAC (56.5% *vs.* 50%). In addition, a major pathological response was associated with improved OS in four included trials.

Additional RCTs and meta-analysis

More recently, three smaller RCTs have been published but only negative results with regard to OS were found by the investigators (17-19). For instance, the Japan Oncology Group analysed 130 patients and found no significant difference in OS between those who received NAC (MVAC) plus RC or RC alone (JCOG0209) (18). However, this study suffered from an early closure due to the slow accrual, which did not allow to reach the initially planned number of included patients. It is noteworthy that a trend toward better OS was observed with the use of NAC (HR =0.65; 95% CI, 0.19–2.18; P=0.07) and the rate of complete pathological response was greater in the NAC followed by RC *vs.* RC alone group (34% *vs.* 9%; P<0.01).

Accordingly, an updated meta-analysis of summary data published in 2016 showed a persistent OS benefit with the use of NAC after including all these negative trials (HR =0.87; 95% CI, 0.79–0.96). This benefit was even greater when only considering patients who received cisplatin-based regimen (HR =0.84; 95% CI, 0.76–0.93) (20).

Long-term oncological outcomes

In 2011, the International Collaboration of Trialists evaluated the long-term oncological outcomes of NAC by updating the preliminary results from the previously described historical RCT (4). After a median follow-up of 8 years, there was a significant OS benefit in patients who received NAC as compared to those who received upfront local treatment. Specifically, a 16% reduction in the risk of death from any cause was observed with the use of NAC (HR =0.84; 95% CI, 0.72–0.99; P=0.037); this translated into an increase from 30% to 36% in 10-year OS. In addition, almost all other oncological outcomes were in favour of the use of NAC, given that such treatment was associated with a 23% reduction in the risk of metastases (HR =0.77; 95% CI, 0.66–0.90; P=0.001) and a 18% reduction in the risk of disease recurrence (HR =0.82; 95% CI, 0.70–0.95; P=0.008). Only the DFS benefit associated with the use of NAC was borderline significant (HR =0;83; 95% CI, 0.68–1.00; P=0.050).

Real-life setting

Numerous retrospective reports have confirmed the benefits associated with the use of NAC in the "real-life" setting. For instance, Zargar *et al.* evaluated pathological downstaging among 935 patients who received NAC followed by RC. Interestingly, the investigators found that the rates of pT0N0 and ≤ pT1N0 pathologic response were 22.7% and 40.8%, respectively (21). Other observational studies focused on identifying the best candidates for NAC prior to RC. For instance, Culp *et al.* proposed a risk-stratified approach for the use of NAC that has recently been validated (22). Specifically, patients were dichotomized in a high- and low-risk groups based on the presence of preoperative risk factors such as ureterohydronephrosis on preoperative CT-scan, lymphovascular invasion, aggressive variant histology, and/or cT3b-T4a disease. Overall, 153 (44.6%) and 190 (55.4%) low- and high-risk patients undergoing RC alone were identified, respectively. At the time of RC, 14.2% of high-risk patients were downstaged. Interestingly, 5-year cancer-specific survival (CSS) rates after surgery were 77.4% *vs.* 64.4% in the low- and high-risk groups, respectively (23). As such, the present results highlight the interest of selecting individuals who may be more likely to experience tumor downstaging and ultimately benefit from NAC.

In fact, downstaging to ypT0 disease at surgery is of upmost importance given that NAC may be only effective for these patients. Indeed, a recent report by Bhindi *et al.* has evaluated the impact of residual disease at surgery after matching 180 patients who received NAC plus RC to 324 controls who received RC alone on the basis of pT and pN stages (24). On multivariable analysis, the investigators found that NAC was associated with a DFS, CSS and OS benefit only in patients who experienced ypT0 disease at RC, while such treatment was associated with adverse oncological outcomes in those with residual disease at RC.

Impact of histological variant

To date, no RCT has evaluated the role of NAC for other histologies than pure urothelial carcinoma. As such, it remains unclear whether NAC should be delivered when non-urothelial features are present at initial diagnosis. Only retrospective reports addressing this topic are available in the current literature. One of the largest scale studies has been recently published by Vetterlein *et al.* (25). Specifically, the investigators compared patients who received NAC followed by RC *vs.* RC alone for several histological variants including adenocarcinoma, squamous cell carcinoma, micropapillary or sarcomatoid differentiations and neuroendocrine tumors. Although individuals with micropapillary or sarcomatoid differentiations and neuroendocrine tumors experienced a decreased risk of upstaging at RC, only those with neuroendocrine tumors benefited from NAC in terms of OS after adjusting for potential confounding.

Biomarkers for patient selection

It is currently recognized that the systematic delivery of NAC for MIBC may result in substantial overtreatment for a subgroup of patients who could be cured by RC alone. In addition, this may lead to adverse oncological outcomes in chemoresistant individuals by unnecessarily delaying RC. Based on these considerations, several biomarkers predicting the response to NAC have been explored over the past decade to improve the patient selection for such treatment.

Specifically, the classification of MIBC into distinct molecular subtypes could represent one of the most promising methods to identify the best candidates for NAC. To date, four reports developed a similar molecular classification distinguishing between basal and luminal subtypes that are associated with patient outcomes (26-29). In addition, Choi *et al.* identified a p53-like subtype, mostly within luminal tumours, that could be associated with a limited sensitivity to MVAC regimen in the neoadjuvant setting (27). This resistance pattern to NAC has further been reported for the gemcitabine plus cisplatin (GC) regimen. On the other hand, basal tumours are characterized by high-proliferative indices and could be more responsive to NAC. These results are concordant with the last study published by Seiler *et al.* who profiled the whole transcriptome of 343 specimens before NAC and subsequently developed a single-sample genomic subtyping classifier (29). The investigators noted that patients with a basal tumor profile had the best response to NAC, confirming that these individuals could represent the best candidates for NAC.

Furthermore, recent immunohistochemistry-based analyses have identified other potential biomarkers associated with response to NAC. For instance, the bladder expression of NrF2, a transcription factor, has been shown to correlate with resistance to cisplatin *in vitro* and worse OS in patients who received NAC (30). Similarly, the bladder overexpression of Bcl-2, an inhibitor of the apoptotic cascade, could help to identify the nonresponders to NAC (31). Finally, the expression of GDPD3 and SPRED1 has also been shown to correlate with the efficacy of NAC (32).

In addition, genomic assessment could provide interesting information for selecting patients for NAC. Specifically, *in vitro* analyses showed that missense mutations of ERCC2, a nucleotide excision repair gene, assessed from exome sequencing, may predict response to cisplatin-based NAC. In addition, mutations in ERBB2/HER2 have been shown to correlate with favourable response to NAC (33). More recently, aberrations in DNA repair of ATM, RB1, or FANCC genes have been found to predict pathological response to NAC and could be associated with an improved OS in patients who received NAC (34).

As such, all these studies taken together support the rational for molecular analysis of MIBC to identify biomarkers predictive of clinical response to NAC. However, only heterogeneous and small sample size studies are currently available and as such, none of the aforementioned biomarkers have been validated for clinical practice.

Comparative effectiveness of chemotherapy regimens

To date, no RCT has compared the efficacy of the different chemotherapy regimens in the neoadjuvant setting. Although it is well-established that cisplatin is more effective than carboplatin for treating urothelial carcinoma in general, there is a lack of level 1 evidence in the current literature to determine the best cisplatin-based combination for NAC. Nonetheless, the MVAC regimen could represent a better alternative than GC, given the greater response rates observed in the metastatic setting (35).

As a consequence, only retrospective reports are available to assess the comparative effectiveness of cisplatin-based regimens for NAC. For instance, Dash *et al.* analysed the oncological outcomes observed after 4 cycles of GC *vs.* 4 cycles of MVAC (36). The proportions of tumor

downstaging and minimal/no residual disease at RC were similar. In addition, there was no substantial difference in DFS, although treatment groups were not directly compared. A recent meta-analysis of all retrospective studies comparing both regimens (including also individuals who received carboplatin instead of cisplatin in combination with gemcitabine) found no significant difference in complete pathological response (20). However, GC/carboplatin was associated with an OS benefit (HR =1.26; 95% CI, 1.01–1.57), which did not reach statistical significance after excluding carboplatin patients (HR =1.31; 95% CI, 0.99–1.74). As such, these results should be interpreted with caution, especially given the substantial biases related to the meta-analyses of retrospective data.

In addition, different modalities for the preoperative delivery of MVAC regimen have been described and analyzed in several phase 2 studies. For instance, Plimack *et al.* evaluated the oncological outcomes obtained after 3 cycles of accelerated MVAC (aMVAC). It is noteworthy that aMVAC regimen was well tolerated, while rates of pT0 disease after RC were similar to those observed in historical cohorts of patients treated with standard MVAC (37). Comparable results were observed in another study evaluating the efficacy of aMVAC (38). An additional phase 2 RCT of aMVAC with bevacizumab showed 5-year OS and CSS rates of 63% and 64%, respectively. Downstaging to pT0N0 or ≤ pT1N0 was observed in 38% and 53% of included patients, respectively. However, bevacizumab was not significantly associated with survival outcomes (39). As such, aMVAC may represent the optimal regimen for NAC but results from several ongoing RCTs comparing different cisplatin-based regimens in the neoadjuvant setting, such as VESPER (NCT01812369), are awaited to draw any definitive conclusion.

AC

Rational

Although the delivery of NAC prior to RC is associated with high rates of pathological downstaging as well as a survival benefit (5), only 1% to 15% of MIBC patients receive such treatment according to the results from population-based studies (40). More recent reports suggest that utilization rates of NAC may be increasing (41,42) but theoretical concerns such as delaying RC while causing unnecessary side effects in chemoresistant patients, represent substantial limitations to the systematic use of NAC. As previously described, multiple biomarkers predicting response to NAC have shown promising results (34,39), but none of them can yet be routinely used for selecting responders with an adequate accuracy. Consequently, a substantial proportion of MIBC patients remains currently chemonaïve at RC and may be suitable for the selective delivery of AC.

The rational for such adjuvant strategy is twofold. First, there is a guarantee that RC is always timely performed without any significant delay that could impact oncological results. Second, the depth of infiltration into the bladder wall, as well as the lymph node status can be accurately determined from the definitive specimen to more adequately guide postoperative treatment decision making. Indeed, it is well-established that pT and pN stages are the most important prognostic factors for both progression and survival after RC (43).

In the late 1980's, Logothetis *et al.* first reported that patients who received cisplatin-based AC for pathologically confirmed extravesical and/or pelvic lymph node-positive had greater 2-year DFS than an historic control group of individuals treated with observation after RC (70% *vs.* 37%; P<0.001) (44). As a result, multiple RCTs have further analyzed the role of AC in this population of patients with high-risk features and several meta-analyses have been conducted to overcome the associated limitations.

Efficacy

Historical RCTs and meta-analyses

The first RCT comparing AC *vs.* observation after RC for locally advanced bladder cancer was published by Skinner *et al.* in 1991 (45); they were rapidly followed by others (46,47). However, all these small sample size RCTs suffered from many methodological limitations. Thus, level 1 evidence supporting the use of AC is more contentious than that previously described for the use of NAC.

In 2005, a first meta-analysis of all published RCTs was conducted by the Advanced Bladder Cancer group from the Cochrane collaboration. Interestingly, the systematic review of the literature identified 11 trials but individual patient data were available for only 6 of them (45-50). Although 90% of patients randomized in cisplatin-based AC RCTs were included in this meta-analysis, only 66% of those randomized in all AC RCTs were considered. More importantly, only two of the selected RCTs completed the planned accrual (49,50). In two other RCTs, around a quarter of individuals allocated to AC did not receive such treatment while many AC patients received regimens other than those described in the study protocol (46,48). Finally, four included RCTs did not report

on the use of salvage chemotherapy for disease recurrence in the group of patients who received initial observation (45-47,49), with a likely consequence of exaggerating the treatment effect of AC.

In spite of these limitations, this pioneering meta-analysis identified an OS benefit in favor of AC *vs.* observation (HR =0.75; 95% CI, 0.60–0.96; P=0.019), which was more pronounced in the sub-group of patients who received cisplatin-based AC (HR =0.71; 95% CI, 0.55–0.92; P=0.010). This corresponded to an absolute improvement in 3-year OS of 9% (95% CI, 1%–16%), which extended to 11% (95% CI, 3%–18%) when considering exclusively cisplatin-based AC. In addition, the use of AC was associated with a DFS benefit (HR =0.68; 95% CI, 0.53–0.89; P=0.004), which was also more pronounced when only considering patients who received cisplatin-based AC (HR =0.62; 95% CI, 0.46–0.83; P=0.001).

Another meta-analysis of summary data from all published RCTs was undertaken by Ruggeri *et al.* in 2006 (51). The investigators found similar results than those reported in the aforementioned meta-analysis based on individual patient data. Specifically, AC was associated with a 26% and 35% reduction in the risk of death from any cause (RR =0.74; 95% CI, 0.62–0.88; P=0.001) and disease recurrence (RR =0.65; 95% CI, 0.54–0.78; P<0.001), respectively.

Nonetheless, other RCTs were conducted (52-54) and further included in an updated systematic review and meta-analysis of summary data published in 2013 (9). In this report, Leow *et al.* built on the 2005 meta-analysis by the Advanced Bladder Cancer group from the Cochrane collaboration to additionally consider the Italian multicenter study (52), the Spanish Oncologic Genito-Urinary Group (SOGUG) study (53), and the US p53 Intergroup study (54). In addition, the update of the 1994 Stöckle RCT (46) published by Lehmann *et al.* in 2006 with a 10-year follow-up after RC (55) was considered by the investigators, who ultimately identified a 23% and 34% reduction in the risk of death from any cause (HR =0.77; 95% CI, 0.59–0.99; P=0.049) and disease recurrence (HR =0.66; 95% CI, 0.45–0.91; P=0.014), respectively. The treatment estimate was more pronounced for both OS (HR =0.74; 95% CI, 0.58–0.94) and DFS (HR =0.62; 95% CI, 0.45–0.87), when considering exclusively cisplatin-based AC. This updated meta-analysis remained limited in terms of sample size with approximately 950 included patients and suffered from the same aforementioned methodological issues inherent to the inclusion of potentially biased RCTs. Thus, the results from the very last RCT by the European Organization for Research and Treatment of Cancer (EORTC) comparing adjuvant *vs.* deferred chemotherapy were largely awaited to potentially fill the gap of rigorous level 1 evidence (6).

EORTC 30994 RCT

The EORTC 30994 is the largest phase 3 RCT comparing adjuvant *vs.* delayed chemotherapy (6). Nonetheless, only 284 patients, of the 660 initially planned, with pT3/T4 and/or pN+ bladder cancer were enrolled to randomly receive either adjuvant (n=141) or deferred (n=143) chemotherapy. After a median follow-up of 7 years, 66 (47%) and 82 (57%) patients died in the adjuvant and deferred chemotherapy groups, respectively. Although there was no significant benefit of AC in terms of OS (HR =0.78; 95% CI, 0.56–1.08; P=0.13), such treatment was associated with prolonged progression-free survival (PFS) as compared to the delivery of chemotherapy at the time of relapse (HR =0.54; 95% CI, 0.40–0.73; P<0.001). This corresponded to an absolute improvement of approximately 16% in 5-year PFS. In post-hoc analyses, Sternberg *et al.* identified a significant interaction between pN stage and the treatment effect of AC on OS (pN– *vs.* pN+; $P_{interaction}$=0.026). Surprisingly, the benefit of AC remained significant only in patients without lymph node involvement at initial diagnosis (HR =0.37; 95% CI, 0.16–0.83; P=0.012), while no difference was noted with the deferred chemotherapy group in those with pelvic lymph node-positive bladder cancer (HR =0.94; 95% CI, 0.65–1.34; P<0.72). In addition, the investigators conducted an updated meta-analysis building on the aforementioned Leow's report (9) and identified an OS benefit (HR =0.77; 95% CI, 0.65–0.91; P=0.001) with the use of AC, which was borderline significant when restricting the inclusion to the Italian, Spanish, and EORTC studies (HR =0.79; 95% CI, 0.62–1.00; P=0.05).

Real-life setting

Given that all these RCTs share the common pattern of incomplete accrual with limited adherence to the treatment protocol, several contemporary retrospective studies have been published with the aim to overcome the underpowered level 1 evidence (56). Unfortunately, these observational reports comparing AC *vs.* observation after RC are likely to be limited by other methodological issues such as selection bias in treatment allocation.

Nonetheless, a collaborative effort among 11 major centers has yielded an international cohort of 3,947 off-

trial patients treated with RC and grouped into quintiles based on risk characteristics for recurrence and death (57). Of these, 932 (23.6%) individuals received AC, which was independently associated with improved CSS (HR =0.83; 95% CI, 0.72%–0.97%; P=0.017). Interestingly, risk groups significantly predicted the magnitude of the treatment effect of AC, given that a greater benefit was observed among patients with more aggressive disease. Specifically, the CSS benefit was only significant in the highest-risk quintile (HR =0.75; 95% CI, 0.62–0.90; P=0.002), which was characterized by the inclusion of a large majority of patients displaying both pT3/T4 and pN+ features at RC.

More recently, a retrospective analysis of 5,653 patients from the National Cancer Data Base (NCDB) who received AC *vs.* observation after RC for pT3/T4 and/or pN+ bladder cancer was published by Galsky *et al.* (58). To date, this is the largest series available with almost 1,300 patients who received AC that was associated with an OS benefit. Specifically, after using several propensity score-based analyses to adjust for baseline patient-, facility- and disease-level characteristics, individuals who received AC were 30% less likely to die following RC as compared to their counterparts who received observation (HR =0.70; 95% CI, 0.64–0.76). This corresponded to an absolute increase of 8% in 5-year OS.

In order to assess the potential benefit of AC, other sophisticated statistical approaches have been used to compare patients who received AC *vs.* observation. For instance, Vetterlein *et al.* performed a propensity-score weighted competing risk analysis showing that AC decreased the risk of cancer-specific mortality (subhazard ratio =0.51, 95% CI, 0.26–0.98; P=0.044) without increasing the risk of other-cause mortality (subhazard ratio =0.48, 95% CI, 0.14–1.60; P=0.233) (59). Similar results were found in the study by Froehner *et al.* (60).

It is noteworthy that observational studies also identified that patients benefiting the most from AC may be those with a low lymph node density as well as those who can receive at least 4 cycles of treatment (61). In addition, PLND at the time of RC has been shown to constitute an important component of advanced bladder cancer management, which could help with regard to indications for AC (62).

Comparative effectiveness of chemotherapy regimens

The GC regimen is preferentially used over the MVAC combination for AC. This is largely based on the results from the RCT by von der Maase *et al.* showing no OS benefit with a regimen over the other for the treatment of advanced or metastatic bladder cancer, and a better toxicity profile for the GC regimen (35). Nonetheless, there is currently no level 1 evidence comparing these 2 regimens in the adjuvant setting. Only retrospective studies suggesting no significant difference in terms of recurrence and survival are currently available (63). Although it is well-established that carboplatin represents a suboptimal treatment for advanced urothelial disease in general, there is insufficient evidence to determine the optimal cisplatin-based AC regimen (64). Nonetheless, in the same manner than for NAC, several ongoing RCTs such as VESPER (NCT01812369) could provide additional guidance in the upcoming years.

Role of AC after NAC and RC

To date, there is no level 1 evidence supporting the use of AC for adverse pathological features at RC despite the delivery of NAC before undergoing surgery, given that all the aforementioned RCTs excluded these patients. However, a small sample size observational study including only 80 patients with pT3/T4 and/or pN+ bladder cancer—29 of whom received AC—found no DFS or CSS benefit with the use of AC in such setting (65). Nonetheless, more recently, a larger NCDB report addressing this topic was published by Seisen *et al.* (66). The investigators identified 788 patients who received either AC (n=184) or observation (n=604) for the same adverse pathological features at RC after NAC. Interestingly, the use of AC was associated with an OS benefit (HR =0.78, 95% CI, 0.95–0.99, P=0.046), although the study was limited by several missing data, such as the detailed chemotherapy regimen or the number/completeness of chemotherapy cycles administered at the time of NAC and AC.

Conclusions

The current literature largely supports the use of NAC before performing RC for MIBC. However, patient selection for such treatment is challenging given that no biomarker predicting the response to NAC can yet be routinely used. On the other hand, evidence supporting the use of AC after RC is more contentious but there is a consensus that it should be proposed to fit patients with adverse pathological features at surgery. While the most effective regimen still remains to be determined for both NAC and AC, the therapeutic landscape for perioperative

management of MIBC could dramatically change in a near future, given the recent advent of immune check-point inhibitors for metastatic disease.

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Footnote

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