Neoadjuvant Treatment for Muscle Invasive Bladder Cancer:

The Past, the Present and the Future

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List of abbreviations:

AC: Adjuvant chemotherapy

BC: Bladder cancer

CRT: Chemo radiation therapy

CB-NAC: Cisplatin based - neoadjuvant chemotherapy

CSS: Cancer specific survival

CMV: Cisplatin methotrexate vinblastine

(dd)MVAC: (dose-dense) Methotrexate vinblastine adriamycin cisplatin

MIBC: Muscle invasive bladder cancer

NAC: Neoadjuvant chemotherapy

NAR: Neoadjuvant radiation treatment

OS: Overall survival

pCD: Pathological complete downstaging (definition for particular studies)

PFS: Progression free survival

PLND: Pelvic lymph node dissection

RC: Radical cystectomy

RCT: Randomized controlled trial

RT: Radiation treatment

TUR: Transurethral resection

Abstract

Background: Approximately half of patients who undergo radical cystectomy (RC) for muscle invasive bladder cancer (MIBC) will succumb to metastatic disease. We summarize the evidence for neoadjuvant radiation- (NAR), chemo- (NAC) and immunotherapy (checkpoint inhibition) prior to RC for MIBC.

Materials and methods: Data were obtained by a search of PubMed®, ClinicalTrials.gov and Cochrane databases for English language articles published from 1925 up to 2017.

Results: NAC usage has increased over the last decade, while NAR is rarely administered. Although NAR results in downstaging, its impact on survival is inconclusive. Based on level I evidence, cisplatin-based NAC (CB-NAC) is considered standard of care in cT2-4aN0M0 MIBC. NAC results in a 6% absolute 10-year overall survival (OS) benefit. In-depth analyses of key randomized controlled trials showed that failure to correct for uniform staging, surgical variation and patient selection compromises the ability to identify factors predictive of response to NAC. The benefit appears to be restricted to patients downstaged to ypT1N0 or less. In these patients 5-year OS is 80-90%. Regarding a number needed to treat of 17, most patients with cT2-4aN0M0 MIBC will be exposed to toxicity without benefit. Possible approaches to reduce overtreatment are suggested in this manuscript and include patient selection, the chosen NAC regimen and emerging molecular data to predict responsiveness to NAC. Neoadjuvant immunotherapy with checkpoint inhibitors is a promising future perspective currently under investigation.

Conclusions: Past studies on NAR show inconclusive results and NAR is rarely administered. Instead, CB-NAC is advised in eligible patients with cT2-4aN0M0 MIBC prior to RC. In the near future, predictive biomarkers will be the key to tailor the use of CB-NAC and reduce harm to non-responders.

Introduction

After radical cystectomy (RC) for muscle invasive bladder cancer (MIBC), approximately half of patients will eventually succumb due to pre-existing metastatic disease or local recurrence[1]. In this context, many efforts have been undertaken to improve oncological outcome by adding various neoadjuvant treatment modalities to RC. Population-based data have shown that use of neoadjuvant chemotherapy (NAC) has significantly increased over the last decade, while neoadjuvant radiotherapy (NAR) is rarely administered anymore[2,3]. Due to inherent study limitations, the robustness of evidence for these treatment modalities can be questioned. One of the main reasons for the slow adoption of neoadjuvant treatment modalities, especially NAC, is the inability to select accurately patients who will benefit versus those who may potentially be harmed[4]. In this review on past, present and future neoadjuvant treatments for MIBC, we summarize the evidence and limitations of studies describing NAR (the past), NAC (the present) and immunotherapy (the future). Two timelines are presented highlighting the landmarks in bladder cancer (BC) care and those specifically for neoadjuvant treatment in MIBC (Figure 1). We also aim to provide guidance for clinicians to further improve individualized treatment for MIBC.

The Past – Neoadjuvant Radiation Treatment (NAR)

As early as 1925, Frank Kidd described the first experiences of radiation treatment (RT) for BC[5]. In eight patients, he observed a decrease in tumor load, a relief of local symptoms and/or an impressive improvement in life expectancy[5]. However, many patients suffered from severe skin burns or mucosal reactions until Henri Coutard developed the principle of fractionation, the basis of current RT, in 1934[6]. In an attempt to decrease local failure and improve survival, urologists and radiation oncologists soon began to use RT as a preoperative adjunct to RC[7].

In the 1960s-80s, multiple efforts were made to evaluate the role of NAR plus RC in MIBC[8-10]. A meta-analysis by Huncharek et al.[11] combined the results of 751 patients from four RCTs assessing 5-year overall survival (OS) for NAR plus RC versus RC alone[8,12-14]. Five-year OS favored patients who received NAR prior to RC, but this finding was not statistically significant (hazard ratio (HR): 0.71, 95%-CI 0.48-1.06)[11]. The largest RCT in this meta-analysis, randomized 475 patients to NAR (45 Gy) plus RC versus RC alone[8]. After definitive surgery, a second randomization to 5-fluorouracil or placebo was conducted. Unfortunately, only 49% of randomized patients completed the prescribed therapy and final survival analysis was conducted only in these patients. Complete pathological downstaging (pCD) to ypT0 was observed in 34% of patients undergoing NAR plus RC and 9% of those undergoing RC alone. Five-year OS in patients receiving NAR was 55% if pCD was achieved, versus 33% for those with residual disease in the RC specimen[8]. These results are severely limited by the absence of an intention to treat analysis. Moreover, the isolated effect of NAR could not be assessed due to the use of concomitant adjuvant chemotherapy (AC). Overall, results from this trial with respect to OS were inconclusive.

A second meta-analysis was conducted with data of the three remaining RCTs. Although these studies were smaller and all independently insignificant, they were of higher quality[11-14]. In contrast, this second analysis did not report an OS benefit for NAR (HR: 0.94 95%-CI: 0.57-1.55)[11]. Of note,

all studies, except for the studies of Smith et al.[12] and Ghoneim et al.[14], used different radiation doses. The study of Ghoneim et al.[14] mostly consisted of patients with squamous cell carcinoma. Furthermore, the radiation techniques would be considered suboptimal by today's standards. These RCTs did not stratify patients according to clinical stage and they suffered from a lack of power to address the potential benefit of NAR[8,12-14].

In a more recent retrospective study, Granfors et al.[15] evaluated the role of NAR in 187 patients treated for cT1-3 BC. They confirmed superior rates of pCD (ypT0) after NAR (39-52 Gy). There was no evidence of residual tumor in 7% of patients after RC alone versus in 57% after NAR plus RC. This effect was most evident in cT3 tumors (pCD in 0% RC alone vs. 56% NAR plus RC). Moreover, patients in this subgroup had superior OS and cancer specific survival (CSS) after NAR, which was not observed for clinically organ-confined tumors[15]. These results suggest enhanced efficacy of NAR specifically in patients with locally advanced disease. In another larger retrospective, single institution, case-control study, Cole et al.[16] compared NAR plus RC (N=301) versus RC alone (N=220) in patients with cT2-4 BC. NAR had a significant impact on local control in patients with cT3b disease (91% vs. 72% local progression-free survival (PFS) after 5 year) and, although not statistically significant, these patients fared slightly better at 5 years in terms of CSS (59% vs. 47%) and OS (52% vs. 40%)[16]. Disparate use of perioperative chemotherapy may have resulted in an underestimation of the effects of NAR in this study.

In conclusion, NAR results in better downstaging, but its effects on survival are inconclusive and its use is generally not advised[17]. The low quality of the studies cited, in combination with recent advances in the care of patients with MIBC, limit assessment of the true impact of NAR. Staging modalities have improved, the extent of surgery has changed (e.g. extended PLND), radiation techniques have advanced and the administration of perioperative chemotherapy has evolved. However, NAR remains a local treatment modality that will not affect distant micro-metastases, so

that perioperative systemic therapy is likely to have a more significant impact.

The Present – Neoadjuvant Chemotherapy

Both neoadjuvant and adjuvant cisplatin-based chemotherapy may be used to eliminate or slow progression of micrometastatic BC[17,18]. While NAC is based on inaccurate clinical staging, AC is more effectively administered in a risk-adapted fashion based on the definitive pathology of the RC specimen. The largest RCT (N=284) observed a 49% 5-year PFS in patients with pT3-4 and/or N1-3M0 BC receiving immediate cisplatin-based AC vs. 30% in those receiving deferred chemotherapy[19]. This translated into a substantial and significant median PFS benefit of 2.0 years, but the study had inadequate power to demonstrate an OS benefit[19]. Meta-analyses have estimated an absolute 5-year OS benefit of 6% with AC which is comparable to the benefit of CB-NAC[19-22]. Recently similar findings were reported in a real world data set[23]. The poor accrual in AC trials (<50% of the intended enrollment) reveals the Achilles heel of the prospective evaluation of this treatment strategy: 25-33% of patients who undergo RC are unable to receive AC due to postoperative problems, such as a decreased performance status or deterioration of renal function[24,25]. In the Nordic Cystectomy Trials and the SWOG-8710 trial 86% and 82% of patients, respectively, underwent RC after randomization to NAC, compared to 87% and 81% after RC alone (Table 1)[26,27]. Furthermore, the BA06-30894 trial, which randomized patients to CB-NAC versus no NAC prior to RC or RT (N=976, of whom 428 had RC), showed that RT can still be offered as a curative treatment option if NAC makes a patient unsuitable for RC[28]. In the BA06-30894 trial, the CB-NAC related mortality rate was 1%[28]. In addition, 4.7%, 3.6% and 2.9% received less than the intended three cycles because of renal toxicity, other chemotherapy related toxicity, or disease progression and early death, respectively[28]. Concerning OS, Grossman et al.[27] reported no difference for patients who had residual disease after either NAC prior to RC or RC alone. In contrast, a retrospective analysis showed that patients with residual BC after NAC have a worse prognosis compared to stage-matched controls undergoing RC alone[29].

Altogether, the likelihood of a patient both undergoing chemotherapy and undergoing RC is greater in the NAC than AC setting. Nevertheless, some important questions remain and are addressed below.

1) What evidence do we have for the application of this potentially toxic treatment?

In Table 1, we have summarized the most relevant findings and limitations of the key RCTs on CB-NAC. A meta-analysis of seven RCTs reported that CB-NAC in cT2-4aN0-XM0 BC resulted in an absolute 5-year OS benefit of 5%[22]. In contemporary MIBC guidelines, CB-NAC is considered the standard of care for patients with cT2-4aN0M0 BC[17]. In the three largest RCTs on CB-NAC, the benefit of NAC appeared to be restricted to the larger number of patients downstaged to (y)pT0 compared to TUR alone (25-38% vs. 12-15%), Table 1[26-28,30,31]. A complete response (ypT0N0) after CB-NAC is associated with a 5-year OS of 80-90%, which drops to approximately 45% for patients with residual carcinoma[26,32]. Subsequent evidence suggests that downstaging to non-MIBC (<ypT2N0) is associated with a comparably favorable outcome, reducing the overall risk of death by 75% (HR: 0.25 (95% CI 0.16-0.40)) compared to patients who still have residual MIBC or nodal disease[33,34].

Due to variations in chemotherapy sensitivity and the potential of cure by RC alone, it is estimated that if all patients with cT2-4aN0M0 BC eligible for NAC did indeed receive NAC, up to 70% of them would be exposed to potential toxicity without clear benefit[4,35]. Notably, a more in-depth analysis of the key published RCTs[26-28], as discussed below, reveals that failure to correct for uniform clinical (nodal) staging, surgical variation (e.g. PLND) and patient selection compromises the robustness of the evidence that has established the OS benefit of CB-NAC for all patients with cT2-4aN0M0 BC[4,36].

The SWOG-8710 trial (N=317) was the first RCT to describe an OS benefit for CB-NAC prior to RC[27]. At a median follow-up of 8.7 years, median OS for patients who underwent CB-NAC plus RC vs. RC alone was 77 vs. 46 months, respectively (p=0.05). In cT3-4aN0M0 BC, NAC was associated with a median OS benefit of 41 months (65 vs. 24 months), which was longer compared to the benefit (30 months; 105 vs. 75 months) reported in patients with cT2N0M0 disease (p=0.05)[27]. The BA06-30894 trial showed an absolute 10-year OS benefit of 6% for those who received CB-NAC prior to definitive local treatment (RC in 428)[28]. Overall, the combined results of the Nordic Cystectomy trials (N=620) did not show any OS benefit for CB-NAC. However, the absolute reduction of risk of death at 5-years in patients with cT3 tumors was 13% in favor of CB-NAC (p=0.019)[26], but there was no difference for cT2 tumors[26].

The results of the SWOG-8710 trial are subject to selection bias due to an accrual period of 11 years and treatment in 126 institutions[36]. The BA06-30894 trial accrued more efficiently (976 patients in 6 years), but is also potentially confounded by accrual across 106 institutions[28]. The main concern with the number of participating institutions is the substantial variability in surgical parameters between trial sites. A secondary ad-hoc retrospective analysis of SWOG-8710 showed that 9% of patients did not undergo PLND and up to 46% received less than a standard bilateral PLND (i.e. node sampling only)[36]. In multivariable analysis, lymph node count was significantly associated with OS and local recurrence, whereas the previously reported beneficial effect of NAC was lost (HR1.0, p=0.97)[36]. The question therefore persists whether NAC would retain its favorable impact on OS if the extent of surgery and especially the PLND were standardized[34]. Similar concerns about the extent of surgery and clinical staging are applicable to the BA06-30894 trial and Nordic Cystectomy trials. Indeed, 25% of the patients undergoing RC in the BA06-30894 trial were staged cNx and the extent of PLND was not described[28]. Clinical nodal staging was not specified in the Nordic trials and patients underwent

only a PLND limited to the obturator fossa. All three of the trials discussed here appear to represent high risk cohorts with poor 5 year survival even with CB-NAC. The 5-year OS for patients with CB-NAC was less than 50% in both the SWOG-8710 and the BA06-30894 trials, and only up to 56% in the Nordic trials[27,28]. However, outcomes were also likely affected by clinical under-staging and suboptimal surgical therapy. In the current era, staging is usually done with at least a CT-scan of the abdomen/pelvis and chest X-ray. In conclusion, the results of these landmark studies may be questioned because clinical and surgical nodal staging was not up to current standards.

2) Which patients are likely to benefit most and from which patients could we consider withholding therapy?

The results of the SWOG-8710 and BA06-30894 trials demonstrated that the largest benefit of CB-NAC is in patients with locally advanced disease (cT3-4a)[26,27,37,38]. The above-cited meta-analyses indicate that the number needed to treat to save one life at 5 years with CB-NAC if all patients with MIBC are treated is 17. A risk-adapted approach could potentially reduce the number needed to treat. However, clinical staging of MIBC is notoriously inaccurate, and any tailoring of CB-NAC to patient risk must be balanced with the potential of under-treatment[39].

The group at MD Anderson Cancer Center (MDACC) has developed a risk-adapted approach to CB-NAC, which they validated in an external patient cohort[35]. In their case-control study 297 patients who underwent RC and PLND without NAC were categorized as having low-, or high-risk MIBC. High-risk disease was present in 98 patients and was defined as the clinical presence of hydroureteronephrosis, cT3-4a BC on CT/MRI or examination under anesthesia, histological evidence of lymphovascular invasion and/or micropapillary / neuroendocrine features

in the TUR specimen. Even though 49% of clinically low-risk patients were upstaged to pT3/4 and/or pN1-3 disease at RC, the 5-year CSS of this risk group was 84%[35]. This study suggests that immediate RC without NAC is an option to reduce the potential toxicity of CB-NAC in patients with low risk cT2 MIBC. AC may still be offered to eligible patients who are upstaged at RC, even though only a minority of such patients received AC in the MDACC series. In Figure 2, we outline the implications of administering CB-NAC only to patients with high-risk disease, instead of all patients with cT2-4aN0M0 MIBC. Assuming that between 1 (scenario B) and 2 (scenario A) out of 5 patients have high-risk disease[2,40,41], chemotherapy toxicity can be prevented in 40-53% of cases while potential benefit is only lost in 10-13%.

3) Which available neoadjuvant chemotherapy regimens should we administer?

Another strategy to reduce toxicity may be the choice of chemotherapy regimen. The landmark trial of Grossman et al.[27] established three cycles of methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) as the NAC regimen supported by the best evidence. The BA06-30894 trial would suggest that CMV would be a reasonable alternative. However, in recent years, the combination of gemcitabine and cisplatin (GC) is used more often than MVAC[33,42] based on results from a RCT in patients with metastatic BC[43]**.** This trial reported significantly lower toxicity profiles for GC but detected no difference in oncological outcomes[43]. RCTs comparing GC versus MVAC or non-cisplatin based regimens in the neoadjuvant setting have not been undertaken. A large retrospective multicenter analysis on contemporary real world data in 935 cT2-4aN0M0 BC patients did not report a difference in pCD (ypT0N0) for neoadjuvant GC (23.9%) versus MVAC (24.5%).[33] RCTs comparing neoadjuvant GC versus MVAC or non-cisplatin based regimens have not been undertaken.

The classic MVAC regimen has been mostly replaced by dose-dense (dd)MVAC in centers that prefer MVAC. ddMVAC is a 2-week-per cycle regimen (instead of 4-week-per-cycle classic MVAC scheme) supported by granulocyte colony-stimulating factor, enabling doubling of cisplatin and doxorubicin dose intensities with reduction of methotrexate dose intensity. This approach decreases the time to RC by 6 weeks compared to the classic MVAC regimen. In a phase III RCT in patients with metastatic BC, ddMVAC had a more favorable toxicity profile compared to classic MVAC, fewer dose delays and higher response rates[44]. In a retrospective, single-center study comparing GC (N=51), MVAC (N=35) and ddMVAC (N=80) in patients with clinically non-organ confined or node positive MIBC, pCD (ypT0N0) was reported in 32% (p=0.845), 20% (p=0.366) and 29% (reference) of patients, respectively[45]. Grade 3-4 toxicity rates for ddMVAC (32%) and GC (44%) were significantly lower than for the classic MVAC regimen (55%)[45]. Since 3 cycles of ddMVAC are 3 weeks shorter than 3 cycles of GC, the authors concluded that ddMVAC should be the preferred option for pre-operative chemotherapy[45]. Moreover, in a recent retrospective multi-center analysis, ddMVAC was associated with a complete response in one third of patients and a partial response (pT1N0) was observed in nearly half of the cases[46]. In the ongoing SWOG-1314 trial, patients with MIBC are randomly assigned to neoadjuvant GC or ddMVAC in order to determine the utility of a gene-expression-based biomarker approach for the prediction of pCD. OS, pCD and toxicity rates will also be compared for both regimens[47].

4) Do we have neoadjuvant chemotherapy options in patients ineligible for cisplatin?

Nearly half of patients with MIBC are not eligible for treatment with CB-NAC due to poor renal function (GFR<50-60ml/min), poor performance status (ECOG-PS≥2), severe (grade ≥2) neuropathy or hearing loss, or heart failure (NYHA-class-III/IV)[25,48]. These patients could be

treated with gemcitabine and carboplatin, but there is no clinical trial data to support this practice. In fact, we know that carboplatin is inferior to cisplatin in multiple trials in the metastatic setting, and the modest benefit observed with CB-NAC would suggest that carboplatin-based NAC would have marginal if any benefit. However, retrospective single-center studies show comparable pCD rates for carboplatin regimens versus CB-NAC[49,50]. Non-cisplatin based regimens are currently only advised for downstaging of a surgically un-resectable tumor[17]. Neoadjuvant therapy for cisplatin-ineligible patients remains a critical unmet need in the care of patients with MIBC.

5) What are tools to predict response to neoadjuvant chemotherapy?

Considering the toxicity of chemotherapy and the potential delay of RC in non-responders[2,3], accurate prediction and evaluation of response is essential. The value of computed tomography to evaluate response to NAC is limited due to the inability to differentiate residual cancer from treatment-induced changes[51]. This results in contradictory clinical and pathological staging in up to 40% of patients[52]. Preliminary studies have shown that novel imaging techniques, such as FDG-PET/CT and diffusion-weighted MRI, might be able to distinguish between responders and non-responders, but further validation is required[53,54].

Gene mutation and expression analyses have recently been described for identification of biomarkers to predict response to NAC. Three groups identified specific gene mutations in MIBC that correlated with response and survival after CB-NAC[55-57]. Van Allen et al.[55] conducted whole-exome sequencing of TUR specimens from 50 MIBC patients who underwent RC after CB-NAC. Nine out of 25 complete responders (ypT0/is) had a mutation in the nucleotide excision repair gene *ERCC2*, but none of 25 non-responders harbored this mutation ($p<0.01$)[55]. Within the unselected Cancer Genome Atlas (TCGA) MIBC patient cohort (N=130), *ERCC2* mutations were present in 12% of

patients[58]. Groenendijk et al.[57] sequenced 178 cancer-associated genes in 94 MIBC TUR specimens. An *ERBB2* mutation was found in 9/38 complete responders (ypT0N0) and in 0/33 non-responders (>ypT2/N+) (p=0.003)[57]. *ERBB2* mutations occurred in approximately 8% of tumors in TCGA-cohort[58]. Groenendijk et al.[57] found six *ERCC2* mutations among responders, but also two in non-responders, both of whom received carboplatin-based NAC. We calculated that if only patients with an *ERCC2* or *ERBB2* mutation would receive NAC, a complete response will be withheld in 32%[55] and 31%[57] of cases, illustrating the relative importance of these two mutations in the absence of other markers. Plimack et al.[56] conducted another interesting study in this domain. In a discovery cohort (N=34), they identified that ≥1 mutations in three genes (*ATM*, *RB1*, and *FANCC*) predicted complete pathological downstaging (ypT0N0) to CB-NAC in 100%[56]. The correlation was less robust in a validation cohort of 24 patients, of whom 11 (46%) had a complete response[56].

Four independent groups have used gene-expression to identify intrinsic subtypes of MIBC[58-61]. Subtypes across these studies showed considerable overlap and distinct responses to CB-NAC[62]. Choi et al.[59] identified a basal, a luminal and a so-called p53-like subtype. Approximately one-third of patients belonged to each subtype[59]. They initially reported that p53-like tumors were more resistant to NAC than luminal or basal tumors[59]. The same group subsequently highlighted the remarkable shift in survival observed for patients with basal tumors[63]. In the absence of NAC, basal tumors were associated with the worst prognosis, but they had the best prognosis after NAC[63].

Recently, Seiler et al.[62] developed a single-sample genomic subtyping classifier based on samples classified according to the molecular subtyping methods of the aforementioned projects. OS and pCD according to subtype (claudin-low, basal, luminal-infiltrated and luminal) were retrospectively compared for 343 MIBC NAC and 476 MIBC non-NAC cases. Luminal tumors had the longest OS with and without NAC. Nevertheless, OS differed according to the response to NAC. Claudin-low tumors were associated with poor OS irrespective of treatment regimen. Basal tumors showed the highest improvement in OS with NAC compared with surgery alone[62].

Altogether, we can conclude that results on gene mutation and expression analyses are promising but still preliminary. Validation in larger prospective cohorts is needed. As previously mentioned, the SWOG-1314 trial started to evaluate the ability of a gene-expression profiling algorithm (COXEN) to predict pathological responses to ddMVAC or GC[47,64]. There are grounds for optimism that predictive biomarkers will soon be used in clinical practice to guide use of NAC in patients with MIBC.

The Future – Neoadjuvant Immunotherapy with Checkpoint Inhibitors

Immune modulation by checkpoint inhibition is an exciting recent development in BC. This treatment modality has mainly been investigated as second line treatment after progression on platinum-based chemotherapy in patients with metastatic urothelial cancer and as first line treatment in ciplatin-ineligible patients[65-69]. Within this setting, reported objective response rates range from 15% to 31%[65-69]. Results on duration of response have to be awaited. In these studies, grade 3-4 adverse autoimmune reactions were present in 5% to 18% of patients[65-69]. Reactions mainly consisted of fatigue, pruritus and rash. However, severe reactions like hepatitis, pneumonitis and colitis also occurred and these prohibited continuation of therapy[65-69]. In the neoadjuvant setting, this could imply definitive surgical intervention has to be discarded. Nevertheless, the success in terms of response rates in the advanced disease state has supported ongoing clinical trials in the adjuvant and neoadjuvant settings in patients with non-metastatic MIBC. Toxicity profiles should be taken into account.

Tumor cells are able to escape from the inherent immunological status – or 'cancer-immune set-point' - of an individual.[70] Current cancer immunotherapy strategies generally aim at restoring T-cell mediated antitumor activity. Expression of cell ligands on antigen presenting cells or tumor cells and engagement with inhibitory receptors on T-cells can withhold either an allogeneic or an antitumor cell response.[70,71] These mechanisms contribute to the protection against autoimmune diseases, whereas tumor cells may exploit their defense mechanisms using these pathways. These T-cell mediated inhibitory pathways are called immune checkpoints and antibodies counteracting the ligand-receptor interaction are called checkpoint inhibitors.[71]

Monoclonal antibodies currently used in BC studies are mainly active in counteracting the checkpoints PD-L1/PD-1 and CTLA-4.[71]

Hypothetically, immunotherapy may be more effective in the neoadjuvant compared to the adjuvant setting since a higher load of tumor antigens is likely to be present if the primary tumor is still in situ[72]. However, it is challenging to conduct trials of neoadjuvant immunotherapy for two principle reasons. Since level-I evidence supports the use of CB-NAC, it is difficult to justify withholding CB-NAC in eligible patients. Furthermore, in the metastatic setting only approximately 20% of patients achieve an objective response to single agent checkpoint blockade, so it is difficult to delay RC for the sake of a systemic therapy that is likely not to help the vast majority of patients. On the other hand, approximately half of patients are ineligible for CB-NAC, and CB-NAC is generally underutilized around the world[2,3,25]. The toxicity of immunotherapy is likely less, although a severe immune-related adverse event prior to RC could preclude subsequent surgery. This might be of special concern in patients who are borderline candidates for RC.

Given the modest improvement of 6% OS after ten years, the associated toxicity and the previously mentioned flaws in the landmark NAC RCTs, we consider it justified to investigate checkpoint inhibition in the neoadjuvant setting. Given the results of the IMVigor210 trial, it is also highly interesting to further clarify the potential role of checkpoint inhibitors in patients with intrinsic subtypes known to be resistant to CB-NAC, for example those with p53-like or luminal-infiltrated tumors[59,62,69]. Currently initiated neoadjuvant phase II trials are investigating safety and downstaging of MIBC prior to RC by checkpoint inhibitors in combination with GC or by using multiple, instead of solo, checkpoint inhibitors[73-76]. Neoadjuvant immunotherapy is likely to have the greatest impact if its use can be guided by predictive biomarkers, such as molecular subtypes[59].

Conclusions

RC alone for MIBC is often insufficient treatment and is associated with a high rate of cancer-specific mortality. Many efforts have been undertaken to improve oncological outcomes by adding neoadjuvant treatment. NAR results in better downstaging but its overall impact in patients with MIBC is inconclusive and its use is generally not advised. The use of NAC has increased in recent years. The absolute OS benefit was between 5-8% in the three landmark RCTs on CB-NAC. In-depth analyses of key randomized controlled trials showed that failure to correct for uniform staging, surgical variation and patient selection compromises the ability to identify factors predictive of response to NAC. However, only a subset of MIBC patients will benefit from CB-NAC, and non-responders are even likely to suffer harm, so that predictive biomarkers will be key to tailoring use of CB-NAC in the near future. For now, selecting patients based on high-risk clinical features (NAC only cT3-4a) might be an approach to reduce overtreatment in the neoadjuvant setting. Looking further to the future, the role of neoadjuvant immunotherapy with checkpoint inhibition is promising and currently under investigation.

Highlights:

1. As approximately half of patients with muscle invasive bladder cancer (MIBC) will develop metastatic disease after radical cystectomy neoadjuvant strategies must be considered.

2. Neoadjuvant radiation yields relevant downstaging but effects on survival are inconclusive and its use is generally not advised.

3. Based on level I evidence, cisplatin-based neoadjuvant chemotherapy (NAC) is considered standard of care in cT2-4aN0M0 MIBC. NAC results in a 6% absolute 10-year overall survival benefit.

4. Predictive biomarkers will be the key to tailor the use of NAC and reduce harm to non responders.

5. Neoadjuvant immunotherapy is a promising future perspective currently under investigation.

Figure legends

Figure 1A. Landmarks in the treatment of organ-confined and metastatic bladder cancer
Abbreviations: BC Bladder cancer; BCG Bacillus Calmette-Guérin; Gem/Cis Gemcitabine/Cisplatin; MVAC Methotrexate Vinblastine Doxorubicin Cisplatin; PLND Pelvic Lymph Node Dissection; RC Radical Cystectomy

Figure 1B. Landmarks in the neoadjuvant treatment of muscle-invasive bladder cancer
Abbreviations: Gem/Carbo: Gemcitabine/Carboplatin; Gem/Cis: Gemcitabine/Cisplatin; MVAC: Methotrexate Vinblastine Doxorubicin Cisplatin

Figure 2. The magnitude of toxicity prevention by selecting only patients with cT3-4aN0M0 bladder cancer for neoadjuvant cisplatin-based chemotherapy, depending on the population: A) 60%, or B) 80% of patients staged cT2N0M0. Scenarios for patients eligible to cisplatin-based chemotherapy prior to radical cystectomy. Abbreviations: AC: adjuvant chemotherapy; NAC: neoadjuvant chemotherapy; RC: Radical cystectomy

Table 1.
Results and limitations of key randomized controlled trials on neoadjuvant cisplatin-based chemotherapy prior to radical cystectomy.

	Nordic I[29]	**Nordic II**[30]	**SWOG 8710**[26]	**BA06 30894**[27]
Patient selection	cT2-4aNxM0	cT2-4aNxM0	cT2-4aN0M0	cT2-4aN0/xM0
Years enrolled	1986-1989	1991-1997	1987-1998	1989-1995
Centers (n)	36	30	126	106
Central pathology	No	No	Yes	Yes
NAC regimen	Cisplatin, doxurubicin	Cisplatin, methotrexate	Methotrexate, vinblastine, doxorubicin, cisplatin	Cisplatin, methotrexate, vinblastine
Cycles (n)	2	3	3	3
NAR	All 20 Gy	-	-	-
NAC + RC vs. upfront RC (n)	151 vs. 160	155 vs. 154	153 vs. 154	491 vs. 485*
RC (n, %)				
NAC+RC	130/151 (86)	132/155 (85)	126/153 (82)	246/284 (87)
Upfront RC	134/160 (84)	139/154 (90)	124/154 (81)	239/277 (86)
RC plus full NAC dose (n, %)	108 (72)	103 (66)	131 (87)**	392 (80)
pT0 (n, %)				
NAC+RC	33/130 (25)	37/132 (28)	48/126 (38)	67/206 (33)
Upfront RC	17/134 (13)	16/139 (12)	18/124 (15)	26/211 (12)
Overall survival (HR, 95%-CI)	0.69 (0.49-0.98)***	0.80 (0.60-1.10)***	1.33 (1.00-1.76) ****	0.84 (0.72-0.99)
Major limitations	1) Preoperative radiotherapy 2) Insufficient clinical nodal staging 3) Insufficient PLND	1) No effect on overall survival 1) Insufficient clinical nodal staging 2) Insufficient PLND	1) Accrual in 126 centers 2) No PLND in 9%, insufficient PLND in 46% 3) NAC did not independently predict OS on multivariable analysis when controlled for extent of PLND[35]	1) Accrual in 106 centers 2) Insufficient clinical nodal staging (cNx in 25%) 3) No analysis of surgical variability 4) Pathology results only available for 417 RC specimens.

* Of the patients 415 were randomized to external beam therapy, including 207 NAC and 208 non-NAC patients.
** At least 1 full dose of NAC.
***Combined data did show a significant effect on overall survival[26].
**** Reversed HR.
CI, Confidence interval; HR, Hazard ratio; NAC, Neoadjuvant chemotherapy; NAR, Neoadjuvant radiotherapy; PLND, Pelvic lymph node dissection; RC, Radical cystectomy.

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