Adjuvant Systemic Therapy for High-risk Muscle-invasive Bladder Cancer After Radical Cystectomy: Current Options and Future Opportunities

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Abstract

We describe the case of a 71-yr-old woman with locally advanced muscle-invasive bladder cancer and stage III chronic kidney disease due to an obstructed nonfunctional left kidney. She was started on neoadjuvant immunotherapy, but had to stop treatment because of acute worsening of renal function. Radical cystectomy was then performed uneventfully, revealing pT3aN1 urothelial carcinoma of the bladder. Adjuvant chemotherapy in high-risk locally advanced bladder cancer after radical cystectomy currently poses several challenges, especially for cisplatin-ineligible candidates. Recent data on adjuvant immunotherapy trials suggest a disease-free survival advantage for this subgroup of patients. The current and future role of immuno-oncology agents in this setting is discussed.

Patient summary: Patients with advanced bladder cancer might benefit from further chemotherapy or immunotherapy following bladder removal, but it is still unclear which patients benefit the most from this strategy. Measurement of biomarkers and scans to show urinary function will probably help in optimising patient selection for this treatment in the near future.

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1. Clinical case presentation

A 71-yr-old female nonsmoker presented with gross haematuria. Her medical history revealed mild hypertension and obesity (body mass index39 kg/m²). Flexible cystoscopy demonstrated a 5-cm solid trigonal mass. A computed tomography scan of the chest, abdomen, and pelvis showed a bladder mass with extramural growth, a left nonfunctioning kidney with severe ureterohydronephrosis, and no evidence of lymph node involvement or distant metastases. Her estimated glomerular filtration rate (eGFR) was 55 ml/min/1.73 m². The patient underwent complete transurethral resection of bladder tumour (TURBT). Pathology showed a high-grade urothelial carcinoma of the bladder invading the muscularis propria, with lymphovascular invasion. A renal scan confirmed a left nonfunctioning kidney.

The patient was offered neoadjuvant immunotherapy with atezolizumab after enrolment in the ABACUS trial (NCT02662309) [1]. She experienced severe renal failure after the initial infusion dose, with subsequent acute kidney injury (interstitial nephritis) requiring hospital admission and treatment discontinuation. Her renal function improved following intravenous steroids, reaching an eGFR value of 33 ml/min/1.73 m². The patient then underwent open radical cystectomy, left nephroureterectomy, and bilateral pelvic lymph node dissection with ileal conduit urinary diversion. No major intra- or postoperative complications were recorded. The final pathology report revealed a pT3a high-grade pure urothelial carcinoma of the bladder, involving two of the 25 lymph nodes removed. Surgical margins were negative. No hospital readmissions were recorded within 30 d from surgery. At 1 mo after surgery her eGFR was 30 ml/min/1.73 m².

2. Clinical case discussion

We discuss the indications and pitfalls of adjuvant chemotherapy (AC) for locally advanced muscle-invasive bladder cancer (MIBC), as well as the current and future role of immunotherapy in this setting.

Current guidelines from major urology and oncology societies provide clear statements regarding the use of perioperative systemic therapy in patients with MIBC. However, neoadjuvant chemotherapy (NAC) is underutilised for several reasons [2]. Adverse events during chemotherapy treatment are frequent, requiring dose reduction or early treatment termination and resulting in poor treatment response. Moreover, up to 50% of candidates who would benefit from NAC are cisplatin-ineligible. Data from clinical trials would support the adoption of NAC [3], but some contemporary retrospective analyses have questioned the overall survival (OS) advantage of NAC, while others have embraced its advantages [4,5].

The management of patients with high-risk MIBC remains an unmet need. To date, several definitions have been applied to determine which patients are considered at high risk of recurrence after RC with curative intent. The definition most commonly used applies to locally advanced MIBC following RC, that is, pT3–4 and/or pN+. Ongoing prospective trials in the adjuvant setting consistently include either ypT2–4 and/or ypN+ cases, or pT3–4 and/or pN+ cases, depending on NAC status.

The optimal adjuvant approach after RC remains to be determined. The novel systemic therapies for bladder cancer have generated a myriad of options in terms of surgical strategies, as well as optimal sequencing schemes.

2.1. AC for high-risk MIBC

The rationale for AC versus observation in patients with prior neoadjuvant immunotherapy for MIBC is under discussion. Final pathology for our case showed pT3a disease with pure urothelial carcinoma and two positive nodes out of 25 removed. Postoperative eGFR was 30 ml/min/1.73 m², and thus stage III chronic kidney disease (CKD) in a patient with obesity would raise concerns. Several groups have sought to identify potential candidates who would obtain a survival benefit from early administration of AC. A major prospective phase 3 trial published in 2015 aimed to provide an answer regarding immediate versus deferred AC in the subgroup with locally advanced MIBC. A total of 284 patients were randomised to receive four cycles of cisplatin-based chemotherapy immediately after RC or at recurrence. At median follow-up of 7 yr, AC improved progression-free survival (PFS) to 47% versus 31% in the deferred treatment group. However, no difference in OS was reported [6]. The main shortcomings of this prospective trial were the premature termination because of slow recruitment (planned sample size 660 patients) and exclusion of patients with prior NAC (current standard of care). A recent report on current practice for patients from a major international urothelial database consortium showed that fewer than 20% of these patients actually received AC. AC provided an increase in time to recurrence even in the group with the worst prognosis (ypT4b/N+); however, no OS benefit was evident [7]. It is well known from retrospective analyses that patients with residual urothelial bladder cancer after NAC, especially those with muscle-invasive disease, have worse outcomes than those immediately treated with RC [8]. The main explanation is that residual cancer may represent chemoresistant disease, which would provide a rationale to support an AC policy for our patient.

The only observational study that has shown an OS advantage for AC is based on National Cancer Data Base (NCDB) data. Initially, 5653 patients with locally advanced bladder cancer were studied using a propensity score analysis for AC versus observation. A total of 23% of patients received AC, and NAC patients were excluded [9]. A later analysis of the same database including only patients with prior NAC was able to confirm an OS advantage when AC was administered [10]. The magnitude of the benefit would possibly be lower for elderly patients. Unfortunately, data on the type of chemotherapy and the number of cycles administered were not available. Similarly, other purpose-built databases have confirmed the survival advantage of AC for chemotherapy-naïve patients [11].
Bladder cancer encompasses a wide variety of histological subtypes. Approximately one-third of newly diagnosed cases involve a non-urothelial variant [12]. All these histological subtypes have been correlated with poorer survival, with a different mutational landscape probably underlying this difference. A subgroup analysis of NCDB data for patients with high-risk MIBC stratified by pure and non-pure urothelial carcinoma failed to show a survival advantage for patients with non-pure urothelial carcinoma receiving AC [13].

In our case, a rationale for AC does exist in view of the locally advanced disease (pT3a, pN1) and an estimated 5-yr OS rate of only 20% for patients without any further treatment. Owing to the patient’s stage III CKD, cisplatin-based regimens would not be indicated, and thus a carboplatin-based schedule, despite its inferior OS advantage, or enrolment in an immunotherapy trial for cisplatin-ineligible patients would be favoured.

2.2. Adjuvant immunotherapy for high-risk MIBC

Immunotherapy has recently brought a paradigm change in the treatment of several malignancies. In bladder cancer, several immunotherapy-based options are currently available for metastatic disease. In the phase 2 IMvigor210 trial, atezolizumab showed a 22% overall response rate, versus 10% for historical cohorts, as first-line treatment for cisplatin-ineligible patients with metastatic urothelial carcinoma [14]. These results were subsequently confirmed among patients with locally advanced or metastatic urothelial carcinoma after progression with platinum-based chemotherapy in the phase 3 IMvigor211 trial [15], with durable responses and a low toxicity profile. Similarly, nivolumab has shown efficacy and safety in the metastatic setting [16].

These data have provided the rationale to test immunotherapy in an earlier phase of MIBC. IMvigor010 was the first large, randomised, phase 3 trial to report outcomes with a checkpoint inhibitor in the adjuvant setting after RC for high-risk MIBC. Two other trials are expected to report outcomes soon (Table 1). IMvigor010 and CheckMate-274 included patients with high-risk urothelial carcinoma of the bladder and upper urinary tract. The primary endpoint was disease-free survival (DFS) and patients with secondary primary tumours or urothelial tract recurrences or pelvic or distant recurrences were included. IMvigor010 showed no difference in DFS between adjuvant atezolizumab and observation (19 vs 16 mo). PD-L1 biomarkers were not useful in stratifying patients potentially benefiting from adjuvant treatment. A slightly higher difference in the rate of adverse events was observed between the two groups, with a 33% discontinuation rate in the atezolizumab arm [17]. CheckMate-274 has recently released preliminary results [18]. Median DFS was 21.0 mo for the 353 participants who were randomly assigned to receive nivolumab 240 mg every 2 wk for 1 yr. This was significantly longer than the median of 10.9 mo for their 356 counterparts receiving placebo, and equated to a significant 30% reduction in the risk of recurrence or death. Patients were stratified by PD-L1 expression and prior NAC. Among patients with PD-L1 expression of at least 1%, adjuvant nivolumab led to an even greater reduction in the risk of recurrence or death of 47% relative to placebo. Data on prior NAC are not available yet. Secondary endpoints of the trial were OS and non-urothelial tract recurrence-free survival (NUTRFS), which includes all other recurrences (mainly pelvic recurrences outside the urothelial tract, and distant recurrences). Both NUTRFS and distant metastasis–free survival were better with nivolumab in both the intention-to-treat and PD-L1 ≥1% populations. The treatment discontinuation rate was 12.8% in the nivolumab arm.

The impact of immunotherapy in the context of minimal residual disease needs to be elucidated. With a recurrence rate of 50–60% in this patient population, DFS seems a clinically meaningful endpoint. The effect size (hazard ratio 0.70) is quite large, so it is likely to translate into an OS that is significantly longer than that observed in the chemotherapy arms.

Table 1 – Phase 3 trials of adjuvant immunotherapy after radical cystectomy for high-risk (pT3–4 and/or pN+) muscle-invasive bladder cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>Inclusion criteria</th>
<th>Randomisation scheme</th>
<th>Primary endpoint</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMvigor010 (atezolizumab) a</td>
<td>ypT2–4 ypN+ UC</td>
<td>Atezolizumab every 3 wk for 1 yr vs observation</td>
<td>DFS</td>
<td>19 mo vs 16 mo (HR 0.89; p = 0.2)</td>
</tr>
<tr>
<td>NCT02450331; N = 809 [17]</td>
<td>pT3–4 pN+ UC</td>
<td></td>
<td></td>
<td>1/3 D/C treatment owing to side effects</td>
</tr>
<tr>
<td>CheckMate-274 (nivolumab) a</td>
<td>ypT2–4 ypN+ UC</td>
<td>Nivolumab every 3 wk for 1 yr vs placebo</td>
<td>DFS all</td>
<td>21 mo vs 10.9 mo</td>
</tr>
<tr>
<td>NCT02632409; N = 709 [16]</td>
<td>pT3–4 pN+ UC</td>
<td></td>
<td></td>
<td>12% D/C treatment owing to side effects</td>
</tr>
<tr>
<td>AMBASSADOR (pembrolizumab) b</td>
<td>Citiplatin-ineligible</td>
<td>Pembrolizumab every 3 wk for 1 yr vs observation</td>
<td>OS</td>
<td>Expected in 2025</td>
</tr>
<tr>
<td>NCT03244384; N = 739</td>
<td>pT3–4 pN+ UC</td>
<td>Citiplatin-ineligible</td>
<td>DFS</td>
<td></td>
</tr>
<tr>
<td>PROFO-302 (infgratinib) b</td>
<td>FGFR3 mutation or fusion required</td>
<td>Infgratinib vs placebo</td>
<td>DFS</td>
<td>Expected in 2024</td>
</tr>
</tbody>
</table>

UC = urothelial carcinoma; DFS = disease-free survival; OS = overall survival; HR = hazard ratio; D/C = discontinued.

a Data reported.
b Ongoing.

benefit. Furthermore, patient-reported outcomes and health-related quality-of-life reports are of extreme interest in this context, since these treatments are offered to patients that are potentially cured by surgery alone.

In our case, no adjuvant chemotherapy was given owing to the lack of data supporting a benefit with carboplatin-based regimens. In view of the CheckMate-274 results, there might be a potential benefit for patients with prior NAC not achieving a pathological complete response (pT0) in receiving nivolumab to delay recurrence.

2.3. Future scenarios in high-risk MIBC

2.3.1. Bladder preservation strategies

Owing to the morbidity and mortality associated with RC and the evidence that up to 30–40% of patients present with pT0 disease at RC, there is a growing interest in selecting patients for bladder preservation. However, uncertainties regarding the similarities between cT0 and pT0 do exist. A combined retrospective study by the Columbia University Medical Center and Memorial Sloan Kettering Cancer Center including 148 patients with cT2N0 receiving at least four cycles of NAC reported high rates of disease-specific survival and OS (90% and 86%, respectively). Of the 71 patients with recurrence, only 11% of the recurrences were MIBC and 75% of cancer deaths were prevented by deferred RC [19]. Of note, up to 90% of patients in this cohort had repeat TURBT. Conversely, other retrospective studies reported an MIBC rate of 51% among cT0 patients after RC with or without NAC [20]. A prospective trial evaluating the role of cystoscopy and systematic bladder sampling in predicting pT0 has recently been published. The results highlight that 25% of patients for whom the urologist reports cT0 actually have residual MIBC. Thus, this prospective evaluation confirms the current limitations of endoscopic assessment in determining a pT0 status [21]. A few prospective studies integrating chemotherapy or immunotherapy with surgery are currently ongoing. RETAIN (NCT02710734) is a phase 2, parallel-arm, multi-institutional clinical trial evaluating a risk-adapted approach to treatment of cT2–3 MIBC. Patients will receive NAC with accelerated methotrexate, vinblastine, doxorubicin, and cisplatin. Pre-NAC TURBT specimens are submitted for deep sequencing of DNA damage response (DDR) genes (ATM, RB1, FANCC, ERCC2). Defects in DDR genes play an important role in treatment response and outcomes in MIBC. DDR mutations are associated with better prognosis in high-risk MIBC. In fact, DDR mutations have been associated with longer OS, and patients carrying three or more DDR mutations are the group with the best prognosis [22]. The primary endpoint in this trial is 2-yr metastasis-free survival. An interim analysis of RETAIN has recently been presented [23]. Of the 77 patients enrolled, 33 had one mutation and 28 entered an active surveillance programme. Of these 28 patients, 14 (50%) experienced recurrence (seven had non-MIBC, five had high-risk MIBC/ metastasis, and two had died of disease). Among all the patients, 50% had an RB1 mutation, for whom the recurrence rate was 62%, and 31% had an ERCC2 mutation, for whom the recurrence rate was 25%. Other similar trials are currently recruiting. ALLIANCE (NCT03609216) is a phase 2 prospective trial that incorporates dose-dense gemcitabine-cisplatin with bladder preservation for patients harbouring DDR gene alterations. The primary endpoint is 3-yr event-free survival. HOOSIER (NCT03558087) is a phase 2 prospective trial of gemcitabine-cisplatin and nivolumab with an endpoint of cT0/Ta rates at 24 mo.

2.3.2. Assessment of tumour response

Multiparametric MRI has been introduced as a noninvasive tool to assess bladder cancer muscle invasion. The Vescical Imaging-Reporting and Data System for scoring was established in 2018 after expert consensus to aid in local bladder cancer staging [24]. Several independent series have subsequently validated this reporting and scoring system and highlighted its utility in predicting the presence of MIBC [25]. A recent analysis of the PURE-01 trial for 123 patients with paired imaging before and after neoadjuvant immunotherapy before RC revealed the relationship between multiparametric MRI and pathological response. The area under the receiver operating characteristic curve for the combination of all MRI sequences for prediction of ypT0 ypN0 and ypT1/Ta/Tis ypN0 response was 0.74 and 0.87, respectively. Moreover, without gadolinium-based sequences, 95% of patients with no radiological evidence of disease were in fact classified as ypT1T1/a/Tis ypN0. This result supports the role of MRI for evaluation of residual disease, avoiding radiation exposure and contrast administration [26].

2.3.3. Prognostic biomarkers in the perioperative setting

Optimising patient selection is key to identifying the best candidates for bladder preservation or adjuvant therapies. Clinically based nomograms after NAC have been published with the aim of identifying which patients might benefit the most from adjuvant treatment [27]. A contemporary approach for patients with MIBC could incorporate biomarkers for response to platinum-based and PD-1/PD-L1-based treatment and evaluation of tumour mutations, followed by application of targeted treatments.

The Cancer Genome Atlas (TCGA) identified at least five different molecular categories for MIBC. The basal-squamous subtype has the strongest immune expression signature and might benefit the most from NAC. The luminal-papillary subtype is associated with targetable mutations (ie, FGFR3) and better prognosis (lower pT0 and pN0 rates at RC). In the TCGA cohort, approximately 12% of MIBC patients had FGFR3 mutations. Retrospective translational analyses have shown that if a mutated clone progresses to MIBC, FGFR3 mutations remain in the invasive compartment and in the metastatic nodes [28]. This finding provides a strong rationale for testing FGFR3 inhibitors in an adjuvant setting in a selected group of patients. Moreover, a multi-institutional collaborative analysis of more than 1000 RC specimens demonstrated that FGFR3 overexpression (28%) was more prevalent than FGFR3 mutations (11%). The subgroup with FGFR3 overexpression may represent a larger nonmutant group of tumours in which FGFR3
signalling suggests a potentially higher percentage of patients who might benefit from anti-FGFR3 treatment [29]. The PROOF-302 trial might provide some answers to personalise the adjuvant treatment for MIBC (Table 1).

Unfortunately, we continue to have limited access to molecular classification in daily routine practice. Incorporation of current knowledge from biomarkers in non-MIBC and MIBC might help to facilitate its clinical applicability.

Circulating tumour DNA (ctDNA) is a promising biomarker in the perioperative chemotherapy setting for both non-MIBC and MIBC. A Danish research collaboration has published encouraging results that require further external validation. A total of 656 plasma samples were drawn from 68 patients with high-risk bladder cancer at the time of diagnosis, during NAC, before RC, and during surveillance. The presence of ctDNA before NAC was a predictor of worse recurrence-free survival and OS. Of note, among patients positive for ctDNA after NAC and before RC, a significantly higher overall 12-mo recurrence rate was observed (75% vs 11%). No pT0 cases were observed among ctDNA-positive patients, and all patients achieving pT0 status were ctDNA-negative. Furthermore, following RC, ctDNA analysis correctly identified all patients who developed metastatic relapse during disease monitoring, with 100% sensitivity and 98% specificity. Expression profiling for tumour subtype and immune signature analyses demonstrated a high contribution of mutational signature associated with ERCC2 status among patients who responded to NAC [30].

A clinical prospective trial (NCT04138628) is investigating early administration of atezolizumab following RC among patients with ctDNA positive. Results are expected within 4–5 yr. Preliminary analysis for the IMvigor 010 trial demonstrated a survival advantage for patients with ctDNA receiving atezolizumab [31].

Tumour mutational burden (TMB), defined as the number of somatic, coding, and base-substitution mutations per megabase of genome examined, is another potential biomarker. Bladder cancer typically carries a high TMB, which provides a rationale for testing TMB as a surrogate for response to immunotherapy. ABACUS data showed that pre-existing T-cell immunity seems to be the driving factor to achieve pT0 status, whereas TMB in association with DDR gene signatures failed to show any predictive role [1]. A recent secondary analysis of the PURE-01 trial has provided a predictive tool in order to elucidate the complex relationship between TMB and PD-L1 expression [32].

In summary, tumour biology following RC in high-risk MIBC might bring a better understanding of which patients benefit the most from available targeted therapies.

3. Conclusions

A perioperative multidisciplinary approach for patients with high-risk bladder cancer should be the standard of care. Current evidence suggests a rationale for adjuvant immunotherapy for patients with high-risk MIBC following RC, with a DFS advantage and acceptable toxicity. Optimising patient selection through novel biomarkers and advanced imaging might improve tumour stratification and drive treatment towards personalised approaches.

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