



## ROLE OF SYSTEMIC CHEMOTHERAPY IN BLADDER CANCER: A REVIEW

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### ABSTRACT

Systemic chemotherapy is integral to the management of muscle-invasive and metastatic bladder cancer (BCa). Neoadjuvant chemotherapy has been increasingly utilized for muscle-invasive BCa over the past several years and several options for cisplatin-based regimens have emerged. Adjuvant chemotherapy may be considered for selected patients who did not receive Neoadjuvant therapy. Systemic chemotherapy added to radiotherapy is a critical component of a bladder preserving approach and superior to radiotherapy alone. Cisplatin-based chemotherapy has been the mainstay for metastatic BCa for more than three decades. Novel targeted agents are in development fueled by the recent molecular characterization of BCa. Recent trials of immunotherapy have demonstrated the possibility of a less toxic and potentially more effective treatment for metastatic disease. It is an extremely exciting time for BCa research, and much needed improvements in systemic treatment are most certainly on the horizon.

**Keywords:** Bladder cancer, Transitional cell carcinoma, Urothelial carcinoma, Chemotherapy, Neoadjuvant therapy, Adjuvant therapy.

## INTRODUCTION

Bladder cancer is the sixth most common cancer in the USA with an estimated 74,000 new case [1]. Although the majority of patients present with on-invasive disease, 10–20 % of these cases eventually progress to muscle-invasive disease. In addition, nearly 30 % of new cases have muscle invasion at the time of diagnosis [2]. Muscle invasion is associated with a high risk of death from distant metastases with level 1 evidence supporting the incorporation of systemic chemotherapy into treatment. Chemotherapy is also the cornerstone of treatment for unrespectable and metastatic disease. This article reviews the use of perioperative chemotherapy in muscle-invasive disease, the importance of systemic chemotherapy in a trimodality bladder preservation approach, and the use of chemotherapy in advanced and metastatic BCa. This is followed by a discussion of the recent exciting developments in molecularly targeted treatments and immunotherapeutic approaches.

### **Perioperative Chemotherapy for Muscle-Invasive Bladder Cancer: Neoadjuvant Chemotherapy:**

The standard of care for muscle-invasive bladder cancer (MIBC) is radical cystectomy with pelvic lymphadenectomy in the last decade, the addition of Neoadjuvant chemotherapy (NAC) has also become standard, based on two randomized controlled trials and a meta-analysis [3].

The Southwest Oncology Group (SWOG) Trial 8710 randomized 317 patients with MIBC to Neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) plus cystectomy versus cystectomy alone. Median survival in the NAC arm was 77 months compared to 46 months in the surgery-alone arm [3].

Cisplatin remains the backbone for all potential NAC regimens. Gemcitabine and cisplatin (GC) combination therapy has become the most widely used regimen in the Neoadjuvant setting. The basis for this combination is a randomized study in the metastatic setting, demonstrating similar efficacy but improved tolerability compared to the MVAC regimen [4].

Dose-dense regimens have also gained momentum as a way to decrease overall time to cystectomy and potentially improve pathologic response rates without increasing toxicity. Choueiri et al. enrolled 39 patients on a phase 2 trial of Neoadjuvant dose-dense MVAC [5]. Four cycles of dose-dense MVAC (dosed every 2 weeks) were given with pegfilgrastim support resulting in a pathologic response rate of 49 %. Ten percent of patients experienced grade 3–4 toxicities. The SWOG is currently enrolling a multicenter trial of Neoadjuvant GC versus dose-dense MVAC prior to cystectomy (NCT02177695) in order to evaluate the predictive capacity of a biomarker called the CO-expression Extrapolation (COXEN) model, which uses preclinical derived gene expression signatures to predict response to different chemotherapy regimens [6]. Although not designed to assess for efficacy differences between these two NAC regimens, it may inform the optimal regimen in subsequent studies.

Unfortunately, there are no proven chemotherapy options for reducing mortality in patients with MIBC who are not eligible for cisplatin. Ideally, such patients should participate in clinical trials but otherwise should proceed to cystectomy without NAC.

## **Adjuvant Chemotherapy:**

Utilization of NAC in MIBC has historically been low with only 1–2% of patients with MIBC receiving NAC in the early 2000s [20]. Although rates of NAC use have been steadily increasing over the last decade in MIBC, utilization remains slow with an estimated 21 % of patients with MIBC currently treated with NAC [7]. Therefore, many patients proceed to cystectomy without preoperative chemotherapy.

No definitive randomized trials provide unequivocal support for the use of adjuvant chemotherapy. However, available clinical trials and retrospective studies suggest that there may be a role for chemotherapy after cystectomy in select patients that were not treated with NAC. Most of the trials evaluating adjuvant chemotherapy in MIBC are small, and many have suffered from poor accrual with initial conflicting results [8]. An updated meta-analysis in 2014 found a similar benefit of adjuvant chemotherapy in pooled data from nine clinical trials [9].

A Spanish Oncology Genitourinary Group (SOGUG) 99/01 study enrolled high-risk patients with MIBC after cystectomy and randomized them to 4 cycles of paclitaxel, Gemcitabine, and cisplatin (PGC) or observation. This study suffered from poor recruitment, and 142 patients were enrolled. However, those that received adjuvant chemotherapy had a significantly improved 5-year survival compared to those that did not.

The patients without pathologic lymph node involvement appeared to derive the most benefit from adjuvant therapy, with one interpretation that 4 cycles of chemotherapy may not be adequate in node-positive patients. The systemic chemotherapy should be offered to eligible patients with high-risk disease at cystectomy, including pT3–T4 or lymph node-positive disease, after a discussion of risks and benefits of adjuvant chemotherapy including a thorough review of the risk of recurrence, toxicities, and acknowledgement of the limitations of the data in the adjuvant setting.

Bladder preservation with trimodality therapy (TMT) is a potential alternative to cystectomy for the treatment of MIBC inappropriately selected patients. This treatment combines radiotherapy, chemotherapy, and as complete a transurethral re-section of the bladder tumor (TURBT) as is safely possible.

## **Chemotherapy for Metastatic Bladder Cancer:**

### **First-Line Therapy:**

The first-line standard of care in metastatic BCa is combination chemotherapy with GC. A randomized phase 3 trial by von der Maase et al. showed GC to have similar efficacy to MVAC with improved tolerability, although it was not powered to show equivalence between the two regimens.

### **Second-Line Therapy:**

Despite relatively high response rates to cisplatin-based first-line chemotherapy, almost all patients succumb to disease. There are currently no Food and Drug Administration (FDA)-approved chemotherapy agents for metastatic BCa in the second-line setting, and only vinflunine is approved for use in Europe based on a 2.6-month survival advantage over best supportive care [10]. Response rates and survival outcomes to standard used second-line treatment are poor. Panofsky PS, presence of visceral metastases, hemoglobin < 10

g/dL, and time from prior chemotherapy <3 months are prognostic in this setting and may be used to inform treatment decisions [11]. The most commonly used chemotherapy in this setting is a single-agent taxane, with both paclitaxel and docetaxel being associated with a modest overall response rate and OS of 6–9 months. However, neurologic toxicity with prior platinum therapy is common and may limit use of taxane in this population. Vinflunine is similarly associated with an ORR of 15–18 % and OS of only 6–9 months [12]. Other chemotherapy options that have limited activity in the second-line setting include ifosfamide, Gemcitabine, and pemetrexed.

Although targeted therapy has become standard treatment in many cancers, no targeted agents have been shown to definitively improve outcome in BCa. The Cancer Genome Atlas (TCGA) comprehensive molecular characterization of 131 MIBC tumors found significant mutations in 32 genes with 69 % of tumors identified as harboring potentially actionable targets [78]. Although study participants were not selected by EGFR status [13]. Seven percent of TCGA tumors had ERBB2 copy number alterations, and HER2 signaling was target Edina trial by Husain et al. with the combination of trastuzumab with Gemcitabine, carboplatin, and paclitaxel in patients with HER2 over expressing advanced BCa, as determined by HER2 immunohistochemistry (IHC), gene amplification via fluorescence in situ hybridization (FISH), or elevated serum Her-2/neu. This regimen showed a 70 % ORR with medians of 14.1 months, which is promising but, given the lack of randomization in this trial, not definitive for an effect of trastuzumab. Despite high rates of IHC positivity, a minority of enrolled patients had positive FISH results, and the optimal method to detect HER2 over expression is not known. Multiple novel agents are being studied targeting the fibro-blast growth factor receptor (FGFR) pathway, which is altered in nearly 70 % of non-invasive BCa and 15 % of MIBC tumors [13].

The complementary vascular endothelial growth factor (VEGF) pathway has also been investigated extensively. Sunitinib did not show an improvement in re-sponse or survival in patients with advanced, previously treated BCa compared to historical controls with PFS of approximately 2 months and median OS of 6–7 months [85]. First-line treatment with Sunitinib in cisplatin-ineligible metastatic BCa showed a PFS and OS of only 4.8 and 8.1 months, respectively [86]. Results with sorafenib were similarly underwhelming [14, 15].

### **Immunotherapy in Bladder Cancer:**

Immunotherapy has emerged as the most promising class of agents in development for the treatment of metastatic BCa after progression on first-line chemotherapy. Many tumor cells express receptors such as programmed death ligand-1 (PD-L1) and cytotoxic T cell lymphocyte antigen (CTLA-4), which inhibit T-cell-mediated tumor cell killing via interaction with T cell receptors.

Anti-programmed death-1 (PD-1) and anti-PD-L1 agents called immune check point inhibitors have demonstrated exciting activity in many human cancers [16]. Initial data show activity of PD-1 and PD-L1 inhibition in metastatic BCa as well [17]. An updated analysis of a phase 1 trial in platinum-refractory metastatic BCa presented at the 2015 ASCO Annual Meeting by Petrylak et al. showed that atezolizumab (MPDL3280A, Genentech) had an ORR of 50 % in PD-L1-positive patients and 17 % in PD-L1-negative patients, with 55 % of all patients showing a reduction in tumor burden with a number of ongoing, durable responses

[17]. Atezolizumab was granted Break through Therapy Designation by the FDA. The phase 2 IM vigor 210 (NCT02108652) results were presented at the 2015 European Cancer Congress, and atezolizumab had an ORR of 18 % based on modified RECIST criteria with higher response rates in PD-L1-positive patients. A phase 3 trial of this agent is underway (IMvigor211, NCT02302807), as well as trials althea adjuvant (Mclvor 010, NCT02450331) and Neoadjuvant settings (NCT02451423).

Similarly, initial data from KEYNOTE-012, a phase-1b study of the PD-1 antibody pembrolizumab (MK-3475, Merck), and showed promising results in PD-L1-positive metastatic BCa with an ORR of 28 % with 64 % of patients experiencing a reduction in tumor bur-den. Median OS was 12.7 months [18]. A phase 3 second-line randomized clinical trial of pembrolizumab against standard cytotoxic chemotherapy has recently completed accrual (KEYNOTE-045, NCT02256436). This agent is also being tested in the first-line metastatic setting for cisplatin-ineligible patients (KEYNOTE-052, NCT02335424) and in the Neoadjuvant setting (NCT02365766). The Bristol-Myers Squibb anti-PD1antibody nivolumab is also being investigated in several cancers including BCa (NCT02387996). The CTLA-4inhibitor ipilimumab underwent evaluation in a first-line trial of Gemcitabine, cisplatin, and ipilimumab for metastatic BCa [19]. This regimen demonstrated an ORR of 64 %, median PFS of 8 months, and median OS of 14.6 months with similar efficacy but more toxicity than historical controls of GC alone. I ipilimumab is associated with more severe immune-related side effects than the newer immune check point inhibitors. Vaccines and other biological compound sare also in development, includingALT-801, a biologic compound of interleukin-2 (IL-2) fused to a human izedsoluble T cell receptor directed against the p53-derived pep-tides expressed on tumor cells (NCT01326871). This com-pound has shown promising early results.

### **Biomarker Development:**

Improved technologies for molecular profiling such as high through put sequencing have launched an integrated approach to drug development with the concurrent discovery of predictive and prognostic biomarkers. This is particularly important in the development of immuno-therapy since responses can be complete and durable, but at present, only a minority of patients responds to treatment. Identifying patients most likely to respond is therefore critical. Immunohistochemical PD-L1 positivity is associated with higher response to immune check-point inhibition, but PD-L1 status does not reliably differentiate responders from non-responders. Tumor somatic mutations can give rise to neoantigens, which peptides are presented on the surface of the cell that are unique to the cancer and may be able to elicit an immune response. A study in melanoma demonstrated that a high tumor mutational load correlates with benefit from immunotherapy with CTLA-4 blockade [20]. BCa has one of the highest mutational burdens compared to other human cancers [21], and this may contribute to the promising activity of immune checkpoint inhibition in BCa. Molecular subtypes of BCa have also recently been identified and resemble the subtypes of breast cancer including Basal and Bluminal subtypes [22, 23]. These sub-types have distinct RNA expression profiles and appear to be prognostic of clinical outcome. The basal subtype is enriched for biomarkers reflective of immune infiltration, potentially suggesting a predictive role for immunotherapy [23].

## CONCLUSIONS

Progress in the treatment of advanced BCa is no longer stagnant. Utilization rates of NAC are rising in response to the unequivocal survival benefit in muscle-invasive BCa. Adjuvant chemotherapy may be considered for select patients who did not receive NAC. The addition of systemic therapy to radiation in bladder preservation approaches improves out-comes compared to radiation alone. Development of targeted agents has been fueled by the molecular characterization of BCa. Immunotherapy with check point inhibitors has promising clinical trial results, and randomized trials are underway. Predictive biomarker development must parallel drug development to best select patients for novel targeted agents and immuno therapies. It is an extremely exciting time in BCa research, and much needed improvements in systemic treatment are most certainly on the horizon.

### Conflicts of Interest:

There authors have no Conflicts of interest to declare.

### Acknowledgements:

This case reporting is supported by the National Natural Science Foundation of China (31700736), Hubei Province Natural Science Foundation of China (2016CFB180), Hubei Province Health and Family Planning Scientific Research Project (WJ2016Y07), Hubei Province Scientific and Technological Research Project (Q20171306), Jingzhou Science and Technology Development Planning Project (JZKJ15063) and the Yangtze Fund for Youth Teams of Science and Technology Innovation (2016CQT04).

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