World Journal of Urology (2019) 37:1767–1772
https://doi.org/10.1007/s00345-018-2480-7

TOPIC PAPER

The role of biomarkers in bladder preservation management of muscle-invasive bladder cancer

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Received: 30 May 2018 / Accepted: 5 September 2018 / Published online: 14 September 2018

Abstract

Purpose Patients with localized muscle-invasive bladder cancer (MIBC) can choose to undergo either neoadjuvant chemotherapy followed by radical cystectomy or radiation therapy-based bladder preservation treatment modality with subsequent close cystoscopic surveillance with salvage cystectomy reserved for patients with evidence of local disease recurrence. At the present time, the decision regarding bladder-directed local therapy for MIBC is based on physicians' and patients' preferences, and does not take into account tumor biology. Predictive biomarkers, once validated, could offer a more patient-centered and biology-driven selection of bladder-directed therapies.

Methods We provide a narrative review of clinical data pertaining to the biomarkers in bladder preservation management of MIBC.

Results There are currently no validated and clinically used biological markers used for stratification of radical bladder treatment and selection of bladder-preserving therapies. This article summarizes biomarkers that could have a potential clinical utility—PD-L1, molecular subtypes, Ki-67, MRE-11 and markers of hypoxia—and offers a hypothetical pathway model for a marker-driven precision management of medically operable patients with a newly diagnosed MIBC.

Conclusion When selecting the optimal cancer treatment, both patient and tumor factors need to be considered. Once validated, biological markers will help clinicians tailor the management of MIBC to individual patients.

Keywords Bladder cancer · Muscle-invasive bladder cancer · Radiation oncology · Biomarkers · Bladder preservation · Precision oncology

Introduction

Identification and validation of a biomarker that would help patients and physicians understand the chances of curing cancer (prognostic marker) and/or offering the most effective treatment algorithm (predictive marker) is a holy grail of translational oncology. Despite a number of potential biomarkers identified by various groups studying patients with muscle-invasive bladder cancer (MIBC) [1], the difficulty in bringing these markers to routine use in clinics is in providing levels of evidence high enough to justify their routine use. In addition, determination and reproducibility of an immunohistochemistry protocol for some of these biomarkers have been difficult across institutions and clinical settings. Predictive biomarker validation requires a randomized clinical trial in order to ensure the patient groups are comparable. The only randomized trial of bladder preservation with RT vs surgery in MIBC—"SPARE" [2]—was stopped early due to poor accrual and patients' non-adherence to allocated treatment arms [3]. Despite numerous retrospective institutional series [4, 5] and meta-analysis [6] showing that bladder preservation with concurrent chemoradiation therapy (CRT) is comparable to upfront cystectomy, neither physicians nor patients are yet prepared for a randomized clinical trial in this field. Therefore, the integration of biomarkers into the upfront treatment decision algorithm is at this point hypothetical and difficult to validate.

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Management of MIBC patients with a bladder preservation approach is also not fully embraced by most practitioners in North America, with National Cancer Data Base analysis in 2012 revealing only 8% of US patients receiving definitive CRT or radiation therapy in the setting of non-metastatic MIBC [7]. Most of these patients are deemed poor surgical candidates by urological oncologists. These patients are much less likely to elect participation in clinical trials investigating prognostic or predictive biomarkers.

In other solid tumors, such as breast cancer, organ preservation—with limited surgery and a combination of radiation and systemic therapy—has been established to be equivalent to radical surgical approaches through randomized clinical trials [8]. In breast cancer, for example, there has been ample opportunity for researchers to identify and validate biomarkers that now form the basis for routine clinical discussion of proper treatment selection: the extent of surgery, the need and sequencing of systemic chemotherapy and targeted agents, and the need and extent of adjuvant radiation therapy, based on genetic and molecular markers.

Bladder preservation treatment modality in North America has been developed through a series of consecutive cooperative group clinical trials conducted by the Radiation Therapy Oncology Group (RTOG) since 1974 [9] as well as meticulous analysis of long-term outcomes among patients treated at Massachusetts General Hospital [10]. In United Kingdom, where popularity of bladder preservation is significantly higher in comparison to North America, with up to 50% of MIBC patients undergoing bladder preservation, radiation therapy in MIBC has been shaped dramatically by two randomized clinical trials—BC2001 [11] and BCON [12]. The BC2001 study randomized patients to RT alone vs RT with systemic chemotherapy (MMC/5FU), whereas BCON study randomized patients to RT alone vs RT with hypoxia modifiers carbogen and nicotinamide (CON). These studies have already provided several biomarkers (such as markers of hypoxia and molecular subtypes, discussed further in this manuscript) and will continue to establish biomarkers that can determine which concurrent therapy, if any, would benefit patients with MIBC undergoing radical radiotherapy.

The biomarkers discussed in this work are not presently used for stratification of radical bladder treatment. Could clinical response to treatment be considered a biomarker in MIBC and used to guide patients in their decision regarding radical cystectomy or bladder preservation approach? The role of neoadjuvant chemotherapy prior to planned bladder preservation is still debated with many experts not recommending routine use of neoadjuvant chemotherapy prior to planned chemoradiotherapy [13]. Neoadjuvant chemotherapy (2 cycles of MCV) prior to concurrent CRT did not improve the outcomes in patients on RTOG 8903, while caused excess toxicity [14]. At the same time, 3 cycles of MCV improved the outcomes prior to radical RT or cystectomy in a randomized clinical trial BA06 30894 [15], the SPARE trial mandated clinical response to neoadjuvant chemotherapy prior to randomization to bladder preservation arm, and 33% of patients enrolled on BC2001 study received neoadjuvant chemotherapy prior to randomization to either radiation therapy alone or concurrent chemoradiation therapy. Delivery of radical curative treatment with RT or CRT was not compromised in patients enrolled on BC2001 due to toxicity or intolerance of neoadjuvant chemotherapy [16]. Some institutions already follow clinical response to neoadjuvant systemic chemotherapy to determine whether to proceed with radical cystectomy in case of poor response, or continue with chemoradiation therapy in case of complete or near-complete response [17]. However, many view response to neoadjuvant chemotherapy as prognostic [18] rather than predictive and do not recommend cystoscopic assessment after completion of neoadjuvant chemotherapy before proceeding with bladder-directed radical therapy.

As clinical data pertaining to the biomarkers in MIBC are extremely limited, our objective is to provide a narrative review of these limited data and suggest how future prospective and precision oncology clinical trials could incorporate these biomarkers into treatment decision algorithms.

Potential biomarkers

PD-L1

Immunotherapy has a well-established role in management of many metastatic solid tumor malignancies and clinical research is underway to determine its role in localized disease—with multiple trials investigating the combination of check-point inhibitors with standard of care treatments—which in MIBC is cystectomy and chemoradiation therapy. A recent small analysis of 72 patients with MIBC revealed a strong association with improved progression-free (60% vs 32%) and overall survivals (75% vs 55%) with negative PD-L1 status among patients with MIBC treated with chemoradiation therapy [19]. This analysis requires large-scale validation, but suggests a potential mechanism-based selection strategy, in which patients with high PD-L1 expressing MIBC tumors are treated with primary immunotherapy, with local therapies—surgery and radiation therapy, coupled with systemic chemotherapy, reserved for patients with poor response to check-point inhibitors. An earlier published report of significantly decreased overall survival in MIBC patients with clinical lymphocytopenia, in comparison to patients without lymphocytopenia (HR 3.9, $p = 0.0028$) [20] suggests a possible interaction between MIBC and immune system, where depletion of lymphocytes by systemic chemotherapy and/or pelvic irradiation may be of a significant

disadvantage in patients otherwise primed for immune-mediated control and eradication of MIBC. Ongoing clinical trials combining check-point inhibitors with either surgery (NCT03472274, NCT03520491, NCT03387761) or chemoradiation therapy (NCT02621151, NCT03419130) will provide critical knowledge on response of both PD-L1 expressing and non-expressing MIBC to these local modalities and appropriate integration of PD-L1 biomarker in the clinical decision algorithm. A large phase III SWOG/NRG 1806 trial studying concurrent chemoradiotherapy with or without atezolizumab is scheduled to open in the next few months and has a robust biomarker validation component. Determination of what constitutes high and low levels of PD-L1 expression for clinical practice—for different immunotherapy agents and with different clinical grade essays—is also imperative prior to integration of immunotherapy biomarkers into clinical care decision.

Molecular subtypes

Prognostication and treatment decisions based on molecular subtypes are by now routine in breast cancer, but are only starting to emerge in the field of bladder cancer. A landmark study [21] has established a clear difference between basal and luminal MIBC in terms of prognosis, whereas a subsequent study [22] revealed that basal tumors are more sensitive to neoadjuvant systemic chemotherapy. While both basal and luminal MIBC responded similarly to radiation monotherapy in BCON randomized trial, addition of concurrent carbogen and nicotinamide (CON)—with intent to mitigate tumor hypoxia—was associated with better survival in patients with basal, but not luminal MIBC [23]. Therefore, pending validation of this treatment strategy in larger clinical studies, basal tumors may be better managed with neoadjuvant chemotherapy followed by concurrent radiation therapy with hypoxia modification (RT + CON).

Ki-67

Proliferation marker Ki-67 is a standard marker used in routine clinical pathology practice, having been shown in various solid malignancies to associate with tumor aggressiveness and propensity to metastasize. High Ki-67 expression was associated with worse bladder cancer-specific mortality among MIBC patients undergoing radical cystectomy in several small single-center studies [24, 25], and subsequently a larger multi-institutional validation study of 713 patients [26]. At the same time, Tanabe et al. [27] reported on dramatic association between high Ki-67 expression and improved cancer-specific survival among MIBC treated with chemoradiation therapy, especially in patients with cT3 and cT4 tumors. One retrospective analysis showed no association between Ki-67 and disease-specific survival in patients treated with either surgery or chemoradiation therapy [28]; therefore, further validation is greatly needed. If validated, this marker could be independently, or as part of the marker panel, used in biological personalization of local therapy strategies, in which patients with high Ki-67 MIBC are recommended bladder preservation option whereas patients with low Ki-67 MIBC are offered upfront cystectomy.

MRE-11

The only validated, but not routinely used, biomarker in MIBC is a DNA damage response-related protein MRE-11, which acts as a sensor of double-strands breaks. Choudhury et al. [29] studied the expression of MRE-11 in two cohorts of MIBC patients treated with radiation therapy and one cohort of MIBC patients treated with cystectomy. Patients in both RT cohorts with high MRE-11 expression levels showed a better cause-specific survival at 3 years in comparison to low MRE-11 expressors (70% vs 43%, $p < 0.05$), whereas CSS was identical among MRE-11 high and low patients who underwent cystectomy. These results were replicated by an independent group of researchers [28]. Among patients treated with concurrent CRT, those with high MRE-11 expression had longer disease-specific survival, whereas among patients who underwent cystectomy this relationship was not seen. Teo et al. [30] used next generation sequencing to analyze the impact of germline variants of MRE-11 encoding gene. The presence of at least one of six rare variants, or of a single nucleotide polymorphism (SNP), was associated with lower 5-year cancer-specific survival in patients with MIBC who were treated with radiation therapy. The analysis of nuclear to cytoplasmic ratio of MRE11 and outcomes in MIBC patients treated on six bladder-sparing North American protocols revealed significant association between low ratio and higher disease-specific survival [31]. It appears that MRE-11 could already be used in clinical practice to help patients and physicians select the most appropriate local therapy—bladder preservation with CRT or radical cystectomy, with prospectively collected outcomes forming the basis for a greatly needed large-scale validation of this biomarker.

Markers of hypoxia

A large randomized clinical trial of RT alone vs RT + CON [12] serves as a great platform for analysis of biomarkers of improved outcomes with addition of hypoxia modifiers. Several independent markers have been retrospectively identified, in addition to the previously discussed molecular subtyping. Eustace et al. [32] showed that the presence of necrosis is predicted for improved survival with the addition of CON to RT, whereas the survival between the two study arms was identical among patients with no necrosis

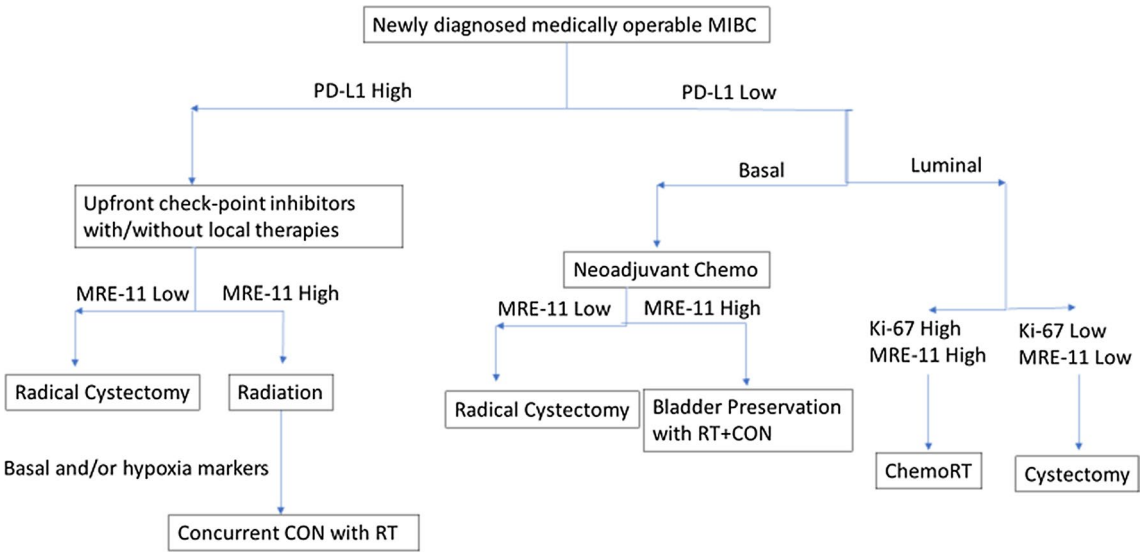

Fig. 1 HYPOTHETICAL and non-validated potential pathway model for a marker-driven precision MIBC multi-disciplinary discussion of treatment strategies for a medically operable patient with a newly diagnosed MIBC. *MIBC* muscle-invasive bladder cancer, *PD-L1* programmed death-ligand 1, *CON* carbogen/nicotinamide gas, *RT* radiation therapy, *chemo* chemotherapy, *chemoRT* chemoradiation therapy

identified in the tumor specimens. Necrosis was independent of molecular subtype. Similarly, individual hypoxia biomarkers, such as Glut 1 and CAIX [33] and HIF1alpha and LDH5 [34, 35], have also been shown to predict for better outcomes with addition of CON to RT. A recently built 24-gene bladder signature was shown to be both prognostic and predictive of benefit from hypoxia modification with the addition of CON to RT [36]. Analysis of clinical outcomes in patients enrolled on BC2001 trial by the presence or absence of tumor necrosis revealed no significant association for necrosis as a predictive or prognostic factor for overall survival, and the benefit of addition of MMC-5FU chemotherapy to radiation therapy was similar in patients with (HR 0.46, $p = 0.05$) and without (HR 0.55, $p = 0.04$) tumor necrosis [37].

Conclusion

The challenge in defining predictive biomarkers is the lack of randomized clinical trials or their inefficiency in delivering answers when conducted. Innovative methodology is slowly changing the clinical research paradigm with precision oncology pathways and real-time analysis of validated early end-points [38] soon replacing phase III trials that take years to accrue and even more years to produce practice-changing or practice-supporting results. These pathways must start with a best data-driven model that undergoes frequent modifications as real-time outcome and toxicity data are analyzed. With AUA publicly supporting multi-disciplinary evaluation and management of patients with MIBC [39], more patients will face the decision on the best treatment algorithm and will demand personalized molecularly driven recommendations, rather than personal biased suggestions from care providers. Figure 1 provides a hypothetical pathway model for a precision oncology multi-disciplinary MIBC tumor board, with explicit understanding of the need for pathways validation and integration into patients' preferences and clinics' expertise. Nevertheless, this is a starting point for further research, debate and evidence-based modifications. Molecularly stratified randomized clinical trials are already being launched in other disease sites—such as the FOCUS4 trial platform in UK designed to identify and register eligible patients with colorectal cancer and enroll them into specific treatment algorithms [40]. Increasingly tumor factors are as important as patient factors when deciding optimal cancer treatment. With concerted efforts among clinicians, patients and patient advocates, MIBC should soon cease to exist in textbooks and guidelines as a single diagnosis, while treatments will become tailored to individual patients based on molecular subtypes and predictive markers, and—of course—personal preferences.

Author's contribution TM Project development, Manuscript writing and editing. AC Project development, Manuscript writing and editing.

Compliance with ethical standards

Conflict of interest T Mitin and A Choudhury have no conflicts of interest to disclose.

Human and animals rights This publication did not involve research involving human participants and/or animals and no informed consent was required.

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