Biomarkers for the prediction of oncologic outcomes in non-muscle invasive bladder cancer: state of affairs and new frontiers

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Introduction

Non-muscle invasive bladder cancer (NMIBC) represents approximately 75% of newly diagnosed bladder cancers (BCa) in western countries (1). Patients with NMIBC have a relatively favorable prognosis, with ten-years cancer-specific survival (CSS) rates varying between 75% and 100%, depending on tumor grade (2). Nevertheless, despite adequate therapy, patients with NMIBC have a long-life risk of disease recurrence and, more importantly, of progression to muscle-invasive bladder cancer (MIBC) (3). While cancer recurrence mainly impacts our patients’ quality of life and the economical burden of the disease, progression to MIBC represents a dramatic event, significantly lowering survival probability and calling for intensified therapy such as radical cystectomy (4). Indeed, patients harboring a NMIBC that eventually progress to MIBC have a worse survival probability compared to a patient who presents with a primary MIBC (5). Because of these reasons, predicting both disease recurrence and progression is of fundamental importance to accurately stratify patients into personalized risk groups for selection of the appropriate treatment strategy, which can range from variable follow up scheduling, from adjuvant intravesical therapy schemes to radical surgery. A personalized assessment of the biologic potential and clinical behavior of NMIBC in every specific patient could allow for an improvement of oncologic outcomes and smart allocation of resources.

Status quo in the prediction of outcomes in NMIBC

Currently, risk-stratification of patients with NMIBC is based on patients’ characteristics and tumor-related features. Based on tumor stage, grade, presence of carcinoma in situ (CIS), tumor size, tumor number and previous recurrence rate, the European Organization for Research and Treatment of Cancer (EORTC) risk tables stratify patients into low, intermediate and high risk for each disease recurrence and progression (6). Since these risk tables were built using clinical trial data of patients treated in previous decades before the widespread use of BCG immunotherapy and re-TUR, their predictive accuracy is limited in contemporary patients. The Spanish Urological Club for Oncological Treatment (CUETO) group tried to overcome these limitations by including only patients treated with BCG and by adding additional features to the model such as age and gender (7). However, the discrimination of even this nomogram remains unsatisfactory when tested in external validation cohorts (8). Both tools exhibited poor discrimination for both disease recurrence and progression.
(0.60 and 0.66, and 0.52 and 0.62, for the EORTC and CUETO models, respectively), underlying the need for better tools incorporating more powerful predictors of oncologic behavior in order to improve NMIBC risk-stratification and therapy.

One hope is to fill the “missing information” by integrating biomarkers that reflect the biological behavior of the cells and its host thereby increasing the capture of the tumors personality. To date, several urinary, blood and tissue markers have been developed and tested with the aim to improving prediction of outcomes and helping with selection, thereby moving a step forward towards the era of personalized medicine. However, due to their suboptimal performances, their role remains, as of today, still limited and none of them is currently recommended by expert guidelines for daily clinical practice (9).

Urinary biomarkers have been used to predict short to intermediate term oncological outcomes as well as response to BCG. A positive fluorescence in situ hybridization (FISH) assay, for example, performed at different time points during BCG therapy, was associated with either disease persistence or recurrence (10,11). Kamat et al. found that a positive FISH both at 6 and 12 weeks resection on BCG therapy can identify patients at higher risk of disease recurrence and progression (12). While promising, validations of these findings are still pending.

Blood-based biomarkers measuring systemic inflammatory response such as the neutrophil-to-lymphocyte ratio (NLR) and the C-reactive protein (CRP) have also been evaluated as predictors of oncological outcomes in NMIBC. Their integration into a model for the prediction of disease recurrence and progression led to an increase in the discrimination of the model (13). These biomarkers are interesting as they may be able to help patients most likely to benefit from systemic immunotherapy such as check-point inhibitors.

A growing body of literature shows that several genes and proteins related to different pathways are not only involved in bladder carcinogenesis but also in its clinical behavior. Consequently, several tissue biomarkers have been tested in a multiphased systematic approach (14). Even if multiple biomarkers, such as cell-cycle markers as well as Ki-67, FGFR3, cadherins, surviving as well as immune and inflammation-related biomarkers have shown to predict NMIBC outcomes, their prognostic value remains suboptimal with only few of them having prospective validation study phases (15-20). Recently, van Kessel et al. prospectively tested a panel of tissue biomarkers comparing their performance to current clinicopathological characteristics for risk-stratification (21). Fresh frozen tumor samples from 1,239 patients with primary or recurrent NMIBC were analyzed for GATA2, TBX2, TBX3 and ZIC4 methylation and FGFR3, TERT, PIK3CA and RAS mutation status. Overall, wild type FGFR3 and methylation of GATA2 and TBX3 were significantly associated with disease progression; the addition of these selected markers to the EORTC risk stratification model increased its accuracy and was able to identify a subset of patients at very high risk for tumor progression. This is probably clinically the most significant finding of this study, as one of the major controversies in NMIBC management is to identify the patients who are most likely to benefit from intensified therapy such as combination systemic therapy or early radical cystectomy.

Conclusions

The search for an ideal biomarker in NMIBC is still ongoing. Given the variable and rich mutation landscape, branched evolution and intratumor heterogeneity of the disease, it is unlikely that a single biomarker is able to address the diverse needs of clinicians. Conversely, biomarkers panels integrating multiple complementary pathways involved in the process of interest (diagnosis, staging, prognosis, and/or prediction) could represent a breakthrough for patients’ risk stratification and treatment selection. Several new biomarkers, probably linked to novel therapies such as PD-L1 expression, will soon enter in clinical practice helping drive a precision medicine approach to BCa. We are slowly but steadily moving towards the era of personalized medicine with biomarkers being the traffic light and/or the target of the personalized medicine voyage in NMIBC.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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