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Seminar article

Blood- and tissue-based biomarkers for prediction of outcomes in urothelial carcinoma of the bladder

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Abstract

Objectives: Urothelial carcinoma of the bladder (UCB) is a highly heterogeneous malignancy that causes significant morbidity and mortality. Standard pathologic features (stage, grade, and nodal status) are insufficient to predict accurately a patient's outcome. Biomarkers could help clinicians provide individualized prognostications and allow risk-stratified clinical decision making regarding surgical and medical treatment. This review summarizes the existing tissue- and blood-based biomarkers in UCB.

Material and methods: A PubMed/Medline search was conducted to identify original articles regarding molecular biomarkers and UCB. Searches were limited to papers published in English. Keywords included urothelial carcinoma, bladder cancer, transitional cell, biomarker, marker, staining, cystectomy, recurrence or progression, survival, prediction, and prognosis.

Results: The articles with the highest level of evidence were selected and reviewed, with the consensus of all the authors of this paper.

Conclusions: There is no doubt that a panel of biomarkers would eventually improve our clinical decision making regarding treatment and follow-up. However, to date, no biomarker panel is yet validated for daily clinical practice.

Keywords: Urothelial carcinoma; Bladder cancer; Molecular marker; Prediction; Prognosis; Survival; Biomarker; Tissue-based; Blood-based

Introduction

Urothelial carcinoma of the bladder (UCB) is a highly aggressive and heterogeneous disease. Better prognostication of clinical outcomes and prediction of response to therapy would help in the selection and timely administration of local as well as systemic therapy in patients with UCB. Unfortunately, pathologic features and imaging are insufficient to allow accurate staging, prognostication, and prediction [1,2]. Furthermore, currently used decision-making tools (e.g., nomograms) have limited ability to capture the true individual tumor biology and clinical behavior [1–4].

Intensive research over the past decade has provided an insight into the molecular pathogenesis of UCB and offers the potential for improving clinical decision making [5,6]. Several tissue- and blood-based biomarkers have been identified. Although none of these biomarkers have reached the clinical validation level, such molecular biomarkers could help clinicians provide individualized prognostications and allow risk-stratified clinical decision making regarding surgical and medical treatment, such as early radical cystectomy (RC) and neoadjuvant or adjuvant chemotherapy [7–11]. In addition, new biomarkers can serve as rational targets for novel therapeutic approaches and allow improved selection of treatment strategies and patients who would benefit from such treatments.

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Table 1
Selection of tissue-based biomarkers for staging and prognostication of bladder cancer

Biomarker	Function	Relevant studies (year of publication)	*n*	Findings
Cell cycle				
p53	Inhibits G1-S progression	Schrier et al. (2006)	80	Altered expression of p53 associated with DR and CSM in pT1N0
		Esuvaranathan et al. [29]	80	Altered p53 not associated with response to intravesical BCG, DR, DP, and CSM in NMIBC
		Moonen et al. [30]	105	No additional value for p53 mutation analysis for high-risk NMIBC
		Shariat et al. [20,26,54]	324	Incorporating p53 expression into clinicopathologic predictive model improved accuracy in RC patients with organ-confined disease
		Shariat et al. [10,22,23,60]	692	p53 as part of biomarker panel improved predictive accuracy for DR and CSM in patients with locally advanced disease after RC
		Shariat et al. [10,22,23,60]	692	Incorporating p53 expression into clinicopathologic predictive model does not improve accuracy in RC patients with locally advanced disease
		Goebell et al. (2011)	3,421	Altered p53 associated with DP in patients with ≥T1 disease
		Stadler et al. [34]	499	p53 status has no association with DR, OS, or adjuvant chemotherapy benefit in Phase III trial of targeted chemotherapy for pT1/T2 patients based on p53 positivity
		Mitra et al. [25]	212	p53 associated with DR and CSM after RC p53 as part of 9 biomarker panel with smoking intensity improved predictive accuracy for DR and CSM after RC
pRb	Cell cycle regulator Sequesters E2F inhibits cell cycle progression	Shariat et al. [10,22,23,60]	692	pRb as part of biomarker panel improved predictive accuracy for DR and CSM in patients with locally advanced disease
		Park et al. [33]	61	No predictive value for pRb expression on IVR or DP in BCG-treated high-grade T1 NMIBC
Ki-67	Marker of cell proliferation	Margulis et al. [37]	713	High Ki-67 labeling index independently associated with DR and CSM in RC patients and improved predictive model for these outcomes
		Shariat et al. [20,26,54]	80	Altered Ki-67 predictive of DR and CSM in patients with pT1 UCB at RC
		Behnsawy et al. [38]	161	No predictive value for Ki-67 expression on IVR in newly diagnosed NMIBC
		Park et al. [33]	61	No predictive value for Ki-67 expression on IVR and DP in BCG-treated patients with high-grade T1
p21	Cyclin-dependant kinase inhibitor regulator at G1 checkpoint	Stein et al. [17]	242	p21 status was an independent predictor of DR and CSM after RC
		Shariat et al. [91,93]	49	Altered p21 expression independently associated with DR and DP in patient with Cis
		Shariat et al. [21,53]	74	Combination of p21 with p53, pRB, and p27 stratified patients into statistically significantly different risk groups for DR and DP in patients with NMIBC
		Shariat et al. [21,53]	300	p21 has cooperative/synergistic action with p53, p27, and pRB
		Shariat et al. [20,26,54]	80	Altered p21 not predictive of DR and CSM in patients with pT1 UCB at RC
		Shariat et al. [10,22,23,60]	692	p21 as part of biomarker panel improved predictive accuracy for DR and CSM in patients with locally advanced disease
p27	Cyclin-dependant kinase inhibitor	Shariat et al. [20,26,54]	80	Altered p27 predictive of DR and CSM in patients with pT1 UCB at RC