ELSEVIER

Urologic Oncology: Seminars and Original Investigations 32 (2014) 222–229

UROLOGIC ONCOLOGY

Seminar article

Urine markers for detection and surveillance of bladder cancer

Evanguelos Xylinas, M.D.[a,1], Luis A. Kluth, M.D.[a,1], Malte Rieken, M.D.[a], Pierre I. Karakiewicz, M.D.[d], Yair Lotan, M.D.[e], Shahrokh F. Shariat, M.D.[a,b,c,*]

[a] *Department of Urology, Weill Medical College of Cornell University, New York-Presbyterian Hospital, New York, NY*
[b] *Division of Medical Oncology, Weill Medical College of Cornell University, New York-Presbyterian Hospital, New York, NY*
[c] *Department of Urology, Medical University of Vienna, Vienna, Austria*
[d] *Department of Urology, University of Montreal Health Center, Montreal, Canada*
[e] *Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX*

Received 12 April 2013; received in revised form 4 June 2013; accepted 6 June 2013

Abstract

Objectives: Bladder cancer detection and surveillance includes cystoscopy and cytology. Urinary cytology is limited by its low sensitivity for low-grade tumors. Urine markers have been extensively studied to help improve the diagnosis of bladder cancer with the goal of complementing or even replacing cystoscopy. However, to date, no marker has reached widespread use owing to insufficient evidence for clinical benefit.

Material and methods: Pubmed/Medline search was conducted to identify original articles, review articles, and editorials regarding urine-based biomarkers for screening, early detection, and surveillance of urothelial carcinoma of the bladder. Searches were limited to the English language, with a time frame of 2000 to 2013. Keywords included urothelial carcinoma, bladder cancer, transitional cell carcinoma, biomarker, marker, urine, diagnosis, recurrence, and progression.

Results: Although several urinary markers have shown higher sensitivity compared with cytology, it remains insufficient to replace cystoscopy. Moreover, most markers suffer from lower specificity than cytology. In this review, we aimed to summarize the current knowledge on commercially available and promising investigational urine markers for the detection and surveillance of bladder cancer.

Conclusions: Well-designed protocols and prospective, controlled trials are needed to provide the basis to determine whether integration of biomarkers into clinical decision making will be of value for bladder cancer detection and screening in the future.

Keywords: Urothelial carcinoma; Bladder cancer; Molecular marker; Biomarker; Urine; Detection; Surveillance

Introduction

Bladder cancer (BC), a highly aggressive and heterogeneous disease, is the most common malignancy of the urinary tract [1]. The global incidence of BC was approximately 357,000 cases in 2012 [1]. Its high incidence, coupled with its high propensity to recur pose an enormous socioeconomic problem. At any point in time, it is estimated that 2.7 million people have the diagnosis of BC in Western countries [2]. Most BC (75%–85%) presents as non–muscle invasive BC (NMIBC) at first diagnosis (Ta, T1, and carcinoma in situ (CIS)) [3,4]. Among these NMIBCs, approximately 70% are Ta, 20% are T1, and 10% are CIS lesions [3,4]. Disease recurrence occurs in up to 80% of patients with NMIBC and is the main problem for patients with Ta NMIBC, whereas disease progression occurs in up to 30% of patients and is the main threat to patients with T1 or CIS [3,4]. NMIBC is particularly sensitive to nuances in care, and each intervention changes the biological and clinical behavior of the disease. Therefore, an in-depth understanding of risk factors and management is necessary to ensure optimal evidence-based clinical care for each patient with NMIBC.

Owing to the lack of disease-specific symptoms, diagnosis and follow-up of BC remain a challenge. Cystoscopy, the gold standard for the detection of BC, is invasive and relatively expensive, thus limiting its use. Although new

* Corresponding author. Tel.: +43-1-40400-2615; fax: +43-1-40400-2332.
E-mail address: sfshariat@gmail.com (S.F. Shariat).
[1] Both authors contributed equally.

1078-1439/$ – see front matter
http://dx.doi.org/10.1016/j.urolonc.2013.06.001

cystoscopy technologies, such as fluorescence or narrow-band imaging, are emerging, the invasiveness and added costs of these procedures further underscore the need for better, simpler, and cheaper diagnostic tests in the management of patients with BC [5–7]. Voided urine cytology is a highly specific, noninvasive adjunct to cystoscopy. It has good sensitivity for detecting high-grade BC, but its sensitivity for detection of low-grade tumors is only 4% to 31% [8,9]. Furthermore, the performance of cytology is dependent upon the level of expertise of the cytopathologist, it is relatively expensive and it is not readily available in all countries. Thus, a noninvasive, highly sensitive, and specific marker for detecting BC could decrease the morbidity associated with cystoscopy, improve patient quality of life, and decrease costs by substituting a less expensive, noninvasive test for the more expensive endoscopic procedure. The clinical scenarios in which such a test could play a role are in the early diagnosis (voiding symptoms, hematuria, and high-risk populations) of BC and the surveillance of patients with previous occurrence of BC.

In this review, we discuss first these 2 clinical scenarios and then report on the performance of the most known commercially available and investigational urinary markers subdivided into cell and protein markers.

Screening and early diagnosis

BC screening could be an indication for the use of a noninvasive diagnostic test [10]. Although the mortality/incidence ratio is higher for BC than for prostate cancer, the comparatively low incidence of BC in the general population, along with the low mortality from BC because of a high amount of cases with nonfatal tumors, has been an obstacle to the development of effective screening strategies for BC. Nevertheless, data from a few screening trials and theoretical considerations on cost-effectiveness issues have revitalized this discussion recently [11–13]. Screening of well-defined high-risk populations with a disease prevalence comparable to tumor entities accepted for screening (e.g. breast cancer or colorectal cancers) may offer a solution to this problem [14]. A recent study, which incorporated data from the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial used simple decision analytic techniques to identify the best candidates for a screening trial [15]. The authors showed that screening for BC can be optimized by restricting it to a subgroup of patients considered to be at an elevated risk. Using a risk stratification tool improved the detection rates when compared with general population (selected on age) and resulted in approximately 25% of the population being screened to prevent 57 invasive or high-grade BC per 100,000 population (while screening the entire population would prevent only an additional 38 cases). As of now, the main risk factors for BC remain age, gender, smoking history, and intensity, as well as some occupational exposures. Determining whether a population is at sufficient risk to justify screening is as important as developing a diagnostic test.

Surveillance

Surveillance of patients with a history of BC is a key area for the use of new markers. This is largely due to the high prevalence and recurrence rate of the disease [4]. Molecular markers may be able to detect BC before they are visually evident [16,17]. However, this causes a significant problem in defining negative tests. Currently, there is no reliable way of separating false-positive tests from true-positive tests when patients do not present with a visually detectable tumor. Theoretically, in the surveillance setting, a marker could both reduce the number of cystoscopies and detect disease recurrence or progression earlier than the traditional tests.

Protein-based urinary markers

NMP22

Nuclear matrix proteins (NMPs) are part of the structural framework of the nucleus and provide support for the nuclear shape. One member of this family, nuclear mitotic apparatus protein 22 (NMP22), is much more prevalent in malignant urothelial cells than in normal cells [18]. Apoptosis is accompanied with a release of NMP22 into the urine, and patients with BC have a significantly elevated concentration of NMP22 compared with their healthy counterparts [18]. The 2 marker tests for BC detecting NMP22 in urine are the original NMP22 BC test kit (Matritech Inc, Newton, MA), a laboratory-based, quantitative, sandwich-type, microplate, enzyme immunoassay, and the NMP22 BladderChek (Alere), a qualitative point-of-care test cartridge containing NMP22 detection and reporter antibodies. Both are Food and Drug Administration (FDA) approved for use in BC surveillance, and the NMP22 BladderChek test is also a approved diagnostic test for BC for individuals who have symptoms of or are at risk for BC.

The sensitivity of the original NMP22 immunoassay ranges from 47% to 100% and its specificity from 60% to 90%, depending on the cutoff value [18–27]. When compared with cytology, NMP22 has a significantly higher sensitivity for detecting BC. The improvement in sensitivity is primarily due to the detection of low-grade and stage BC [28–30]. Similarly to all markers, there is also a possible effect of marker sensitivity based on whether the marker is used for detection or surveillance. However, this may be related to the fact that tumors are larger at diagnosis and have a more advanced stage than those detected during surveillance [28]. Moreover, in the 2 large prospective multicenter studies, NMP22 BladderChek test had a