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Urologic Oncology: Seminars and Original Investigations 24 (2006) 326–337

UROLOGIC ONCOLOGY

Seminar article

Molecular markers in bladder cancer: A critical appraisal

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Abstract

The diagnosis of both primary and recurrent bladder tumors currently relies upon the urine cytology and cystoscopy. Neither of these diagnostic tools is completely accurate. Prognostication of bladder cancer is largely based on pathologic tumor grade and stage. Over the past 2 decades, there is accumulating evidence that like many other cancers, bladder cancer, too, has a distinct molecular signature that separates it from other cancers and normal bladder tissue. Bladder tumors of different grades and stages even possess unique, and specific genotypic and phenotypic characteristics. Although recognition of several of these molecular alterations is possible by analyzing tumor tissue, urine, and serum samples, few if any of these "molecular markers" for bladder cancer are widely used in clinical practice. These markers include some that can be applied during the diagnostic work-up of symptoms (e.g., hematuria), those under surveillance for recurrence of superficial disease and forecasting long-term prognosis, or response to chemotherapy. In this review of molecular markers for bladder cancer, effectiveness of markers in each of these categories that are identifiable in the urine of patients with bladder cancer was examined. Many of the diagnostic markers appear to hold an advantage over urine cytology in terms of sensitivity, especially for the detection of low-grade superficial tumors. However, most markers tend to be less specific than cytology, yielding more false-positives. This result is more commonly observed in patients with concurrent bladder inflammation or other benign bladder conditions. Although there are several candidate markers for assessing prognosis or response to chemotherapy, studies of large patient populations are lacking. Further studies involving larger numbers of patients are required to determine their accuracy and widespread applicability in guiding treatment of bladder cancer. © 2006 Elsevier Inc. All rights reserved.

Keywords: Urine markers; Bladder cancer; Diagnosis

Introduction

Bladder cancer was the fifth most common malignancy in European men in 1995 and the sixth leading cause of cancer mortality [1]. In the United States, 63,210 new cases are expected, with 13,180 deaths anticipated in 2005 [2]. A MEDLINE search of the literature on markers and bladder cancer from 1990 to 2004 yielded 1851 English language reports, of which 23% were regarding urine markers. This finding represents a 144% increase in the annual number of published reports. This review will focus only on urine-based diagnostic and prognostic markers of transitional cell carcinoma (TCC) of the bladder.

An ideal bladder cancer marker should be objective, noninvasive, easy to administer and interpret, and possess high sensitivity and specificity. Microscopic hematuria detected by dipstick can be fairly accurate in detecting bladder cancer, with a sensitivity of 40% to 92% and specificity of 51% to 96% [3–7]. However, up to 25% of patients with bladder cancer may not have hematuria, even when they have a known bladder tumor [8]. Cytology has low sensitivity and specificity, particularly for low-grade tumors [9–14]; its results are not available immediately and are interpreter dependent. Cystoscopy, which is used in most studies of diagnostic markers as the reference standard, is itself not always accurate, with a sensitivity as low as 73% [15] and specificity of 37% [16]. Estimates of false-negative cystoscopy range from 10% to 40% [17,18]. The low effectiveness and invasive nature of conventional methods in the diagnosis of bladder cancer have prompted the search for newer and better ways to diagnose the disease.

When used for screening high-risk individuals or for a diagnostic work-up of symptoms, a marker has to have a high sensitivity and positive predictive value (true positives/true positives + false positives). When used for surveillance, particularly in lieu of cystoscopy, a marker should possess a high negative predictive value (true negative/true negative + false negatives). A quantitative marker that correlates to tumor burden or grade would be best suited for

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doi:10.1016/j.urolonc.2005.11.023

Table 1
Sensitivity and specificity of urine based bladder markers

Bladder cancer marker [references]	Mean sensitivity (range)	Mean specificity (range)
Cytology [7,9,10,13,7,30–46]	48.00% (28%–76.47%)	95.72% (81%–100%)
NMP22 [9,10,20,24,26,28,30,32,40–55]	67.49% (31%–91.7%)	74.38% (5.1%–94.3%)
BTA stat [6,8,30,33,36,49,56–63]	68.71% (52.8%–89%)	73.67% (54%–93%)
BTA TRAK [5,25,33,49,59,64–66]	61.96% (17%–77.5%)	73.59% (50.5%–95%)
Telomerase [4,6,9,13,67–71]	72.4% (46%–92%)	87.15% (69%–99%)
Hyaluronic acid and hyaluronidase [62,72,73]	94% (91%–100%)	80.93% (70%–88.8%)
Flow cytometry and Quanticyt™ assay [28,30,35,37,74]	58.08% (45%–72%)	80.62% (70.6%–93%)
Fluorescence in situ hybridization [6,37,75]	77% (73%–81%)	98% (96%–100%)
ImmunoCyt™ [39,75–77]	58.2% (38.5%–86.1%)	78.77% (73%–83.9%)
Cytokeratin 20 [38,78–82]	82.83% (71%–94.4%)	73.37% (36%–96.7%)
Cytokeratins 8 and 18 (UBC) [33,51–53,83]	60.7% (48.7%–70%)	83.82% (72%–95%)
Lewis X antibody [34,61]	87.1% (79.8%–94.4%)	61.65% (36.9%–86.4%)
Hemoglobin dipstick [4–7]	71.2% (47%–92.6%)	67.27% (51%–84%)
CYFRA 21-1 [51,84]	74.15% (69%–79.3%)	91.3% (88.6%–94%)
Survivin [85]	64%	93%

staging and assessing response to intravesical or systemic therapy.

Markers for diagnosis of primary or recurrent tumors

NMP22 test

NMP22 (Matritech Inc., Newton, MA) is a nuclear mitotic apparatus protein found in the nuclear matrix of all cell types. Patients with bladder cancer may have urinary NMP22 levels that are 25-fold higher than normal individuals [19]. Using 10 U/ml as a normal cutoff, the test can identify those patients who are likely to have invasive disease or those who subsequently develop local recurrence [20]. Reports regarding the grade and stage-based sensitivity of NMP22 have not been consistent [8,21,22]. The presence of cystitis, hematuria, and pyuria may also increase NMP22 levels in patients without bladder tumors [23] but appear to have no impact in patients with bladder tumors. In patients without a prior diagnosis of bladder cancer, NMP22 had a higher sensitivity (80.9% vs. 40%) but a lower specificity (64.3% vs. 100%) than voided urine cytology [11,24], although not all data support these conclusions [25,26].

In patients with risk factors/symptoms suspicious for bladder cancer, the NMP22 BladderChek test, a point of care test, has shown a sensitivity of 56% compared to 16% for urine cytology [27]. The specificity of NMP22 BladderChek was comparable to that of cytology (90% vs. 99%). Patients with neobladders appear to have a high level of NMP22 in the urine [28,29]. Table 1 summarizes the results of many of the studies available on the use of NMP22 for the detection of bladder cancer. The positive predictive value of this test is low, rendering it less useful for initial diagnosis or screening. Because of its high negative predictive value, it would be more useful in monitoring patients for recurrence.

Recent studies indicate that using a combination of markers, including NMP22, in a neural network analysis format can reduce the costs of standard diagnostic evaluation for bladder cancer by almost 50% [7]. Using a nomogram based on patient age, gender, urine cytology, and urinary NMP22 levels, Shariat et al. [86] were able to predict 84% of tumors of all grades/stages and 87% of high-grade, superficial tumors. There was a 17% variation in the predictive accuracy of the same model between institutions, suggesting that differences in test interpretation and cystoscopic findings will influence the accuracy of prediction by the nomogram. It may be necessary to reduce the cutoff values to 5 U/ml in the surveillance setting to maximize sensitivity because NMP22 levels are correlated with tumor size, and recurrent tumors generally tend to be smaller [87]. The NMP22 BladderChek test is easy to administer and relatively inexpensive (Table 2). As all other Food and Drug Administration (FDA) approved urinary markers for bladder cancer, the NMP22 test is only approved for use as an adjunct to current diagnostic methods, such as cystoscopy. We are currently investigating its possible use as a substitute to cystoscopy in monitoring patients with low-risk superficial bladder cancer.

BTA test

The original BTA test (Bard Diagnostics, Redmond, WA) detected presence of the basement membrane antigen in urine was more sensitive than cytology, but results were inconsistent [9,31,89–92]. The subsequently introduced BTA stat (qualitative point of care test) and BTA TRAK (quantitative) detect a human complement factor H-related protein produced by human bladder cancer cells, which enhances degradation of some other complement factors [93]. The BTA stat test yielded a sensitivity of 58% and a specificity of 95%, which decreased in the presence of coexisting non-neoplastic urologic conditions to as low as 50% [57]. Ellis et al. [64] reported a sensitivity of 68% for the BTA TRAK test. Most studies indicate a higher sensitivity for BTA stat compared to cytology but a lower spec-

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