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The Impact of Monoclonal Origin and Intraluminal Seeding Mechanism on Management of Non-Muscle Invasive Bladder Cancer: Needs for More Preoperative Adjuvant Intravesical Immune-and/or Chemo-Therapy

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Abstract

Bladder cancer is a common disease, worldwide it is ranked as the seventh and the seventeenth most frequent cancer worldwide in men and women respectively. Based on the histopathology (grading and staging), bladder cancer can be classified into non-muscle invasive (superficial) and muscle-invasive disease. The natural history of the superficial tumors differs from the muscle invasive ones. Most non-muscle invasive tumors are characterized by multiplicity, high recurrence rate, and heterogeneous natural history. According to many investigators, the multifocal nature of non-muscle invasive uroepithelial cancer, together with a propensity for recurrence (polychrono topicity) is the results of intraluminal seeding of viable detached malignant cells that results in genetically monoclonal multiple tumors. Thus, the intraluminal shedding and implantation of viable tumor cells have been proposed as the mechanisms responsible for both synchronous and metachronous multifocal bladder tumors. These findings are of considerable relevance for therapeutic strategies, suggesting that complete endoscopic removal of the primary tumor is often not enough to treat even non-muscle invasive bladder cancer because by, or during, the time of initial treatment, several micro satellite tumors are already implanted in the bladder. Therefore, additional measures to prevent tumor cell seeding and growth of the already implanted ones may reduce the recurrence rate of non-muscle invasive bladder cancer.

The intraluminal seeding mechanism of synchronous and/or metachronous tumors enforces more emphasis on intravesical adjuvant therapy in superficial bladder cancer, including the use of intravesical chemo- or immunotherapy and long interval follow-up for those patients. Adopting such therapeutic strategy may improve morbidity and mortality of superficial bladder cancer.

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Introduction

Bladder cancer is a common disease, both in industrial and developing countries. Cancer of the bladder is estimated to be the ninth most common cause of cancer worldwide and the 13th most numerous cause of death from cancer [1]. It is the 7th most common cancer in males and the 17th most common in females worldwide [2]. Family history is associated with an approximately two fold increased risk in cancer [3].

The disease is highly heterogeneous considering their natural history, histological, and geographic characteristics. Although, 75–85% of patients with bladder cancer present with a disease that is confined to the mucosa or submucosa, known as the non-muscle invasive bladder cancer (NMIBC) [4], the disease still represents a major therapeutic challenge since 30% of urinary tract TCCs are found as multiple tumors at the time of diagnosis, and 70% of the non-muscle invasive bladder tumors recur after initial cystoscopic resection [5,6] of these recurrent cases, 80% remain superficial throughout the life of the patient, whereas 16% to 25% eventually recur as higher grade and/or stage tumor(s) [7,8]. A small percentage (10–15%) of all noninvasive (superficial) lesions will progress to muscle-invasive disease, and genetic instability is crucial to this progression [9]. Even tumors of same pathologic stage, may follow very different clinical courses. Current prognostic markers (tumor grade, multiplicity, tumor shape, location, and presence of carcinoma *in situ* (Cis) are of limited value [10] why it is difficult to predict the clinical course, especially for superficial bladder tumors. However, the high rate of recurrence and disease progression may indicate inadequate current therapeutic modalities.

The multifocal nature of bladder cancer, the tendency for recurrence (polychrono topicity), and the dysplastic changes that usually seen surrounding bladder tumors [11], have been interpreted as evidence of field disease [12]. According to this field disease theory, the entire epithelium is tumor-prone in the sense that multiple polyclonal primary lesions are likely to emerge from it, either synchronously or metachronously [13]. The alternative, monoclonal view assumes a common clonal origin of all multiple and/or recurrent tumors in each patient, implying that these macroscopically distinct lesions develop as the result of intraluminal seeding of cancer cells shed from the primary tumor. Support for the monoclonal hypothesis has come from molecular, cytogenetic, and molecular cytogenetic studies [14,-16]. Epidemiologic and clinical data have shown that patients with ureteral or renal pelvis tumors have a higher (40%) risk of having tumor(s) also of the bladder, and if carcinomas of both the renal pelvis and the ureter are present, the probability of having BC increases up to 75% of cases [17,18]. The proportion of patients with non-muscle-invasive bladder cancer developing metachronous upper urinary tract-TCC varies from 0.7 to 4% [19]. The present report reviews the previous reports on clonal origin of multifocal uroepithelial carcinoma and the implication of their findings on the treatment and follows up of patients with non-muscular invasive bladder cancer.

Material and Methods

Several reports on the clonal origin of multiple macroscopically distinct uroepithelial tumor lesions (bladder tumors, ureteral tumors, recurrent bladder tumors), obtained from the same patients have been published. Those studies used various analysis techniques such as cytogenetic analysis [15], comparative genomic hybridization (CGH) technique [16], microsatellite markers to examine genetic alterations [20,21], methylation patterns of the androgen receptor gene (HUMARA) located at the X-chromosome [22,23], and CD44 alternative splicing patterns [24]. Other studies used molecular analyzed of p53 tumor suppressor gene mutation by PCR-SSCP and sequencing [14,25-27]. Loss of heterozygosity (LOH) assays and X-chromosome inactivation [28], and most recently exome sequencing [29].

In most of the studies, the synchronous and/or metachronous multifocal tumors were carefully, separately collected and processed. For studies using X-inactivation only tumors from female patients were analyzed. The cytogenetic clonality criteria and the karyotype descriptions were done according to the ISCN recommendation [30]. The Grading and staging were done according to WHO (1973) criteria and the UICC (1978) tumor-node-metastasis (TNM) classification system, respectively [31].

Results

The cytogenetic analysis of multiple tumors obtained from each patient, including recurrent ones have shown consistent cytogenetic monoclonality seen as almost identical karyotypes demonstrating their common clonal origin. CGH Studies showed that all tumors derived from the same patient shared a set of identical alterations suggesting common clonal origin.

TP53 mutation analysis revealed identical *TP53* mutations and protein over expression in individual tumors in molecular studies. The results provide further strong evidence for a monoclonal origin of multifocal bladder cancer. It also suggests an intraepithelial migration of tumor cells carrying specific chromosomal aberrations. The same conclusion reached in studies using methylation analyses. All tumors were monoclonal as indicated by unbalanced methylation. Furthermore, same methylated allele has been detected in multiple recurrent or multifocal tumors from any given patient, indicating their identical clonal origin. Studies used loss of heterozygosity (LOH) technique showed nearly identical pattern of allelic loss indicating the common clonal origin. Phylogenetic analysis of high confidence single nucleotide variants (SNV) demonstrated that the sequenced multifocal bladder cancers arose from a clonal origin in the tumors of each patient.

Discussion

Although studies investigated the clonal origin of bladder cancer tumors have used various techniques, they reached the same conclusion that multifocal uroepithelial tumors have a monoclonal origin that arise via intraluminal seeding of viable cancer cells shed from the original tumor. The results of all studies suggested that the later lesions develop also from cells shed from so-called second primary tumors, and according to genetic evolution, the seeding of tumor cells is a comparatively late event that succeeds the acquisition by them of multiple secondary genetic abnormalities [32,33].

Cystoscopic examination has a major limitation as a follow up tool because tiny papillary tumors are easily overlooked, Cis, dysplasia, and cases of microscopic recurrences cannot be detected [34]. Urine cytology has low sensitivity for well-and moderately differentiated cells that represent around 75% of all bladder cancer at diagnosis [35]. Positive urine cytology ranged between 10% and 90% based on the grade of the tumors [36]. Even when random biopsies are taken, only 24% of the cases can be diagnosed. Based on FISH studies using in the majority of the cases microscopic recurrences were detected as malignant cell in urine samples collected from patient with previous history of bladder cancer and present not so ever clinical or radiological evidence of recurrent disease [37]. This may indicate that in fact residual cancer following transurethral resection is more than one would expect. However the logical question should be whether all these so called micro-recurrences will give rise to clinical recurrences. No present answer available but epidemiological data suggesting this possibility. Another strong evidence arrived from analysis of synchronous and metachronous tumors along the urinary tract system showed monoclonal origin indicating the intraluminal seeding mechanism as a mechanism responsible behind high rate of recurrences and multifocality often seen in uroepithelial tumors [24,26]. Epidemiological data revealed that an upper urinary tract tumor is associated with a 75% probability of finding tumor(s) also in the bladder, whereas the risk of developing a ureteral tumor following the diagnosis of a bladder tumor is only 4% [18]. Studies investigated the clonal origin of associated bladder tumor(s) with ureteral tumor in the same patient concluded a downstream shedding of cancer [15]. Thus such data argue against the regrowth of a new tumor at a site different from the primary and instead favor the shedding and intraluminal seeding hypothesis [16].

By ruling out the field cancerization view it is then clear that most tumors including superficial papillary ones are in fact inadequately treated. Clinical studies showed that after standard transurethral resection, about 60%of superficial tumors recur as tumors of the same grade and stage, whereas 25% relapse with more advanced and aggressive forms of cancer [35].

Because intraluminal shedding and implantation of tumor cells is

the mechanism responsible for both synchronous and metachronous multifocal uroepithelial carcinomas, it is beyond doubt that complete endoscopic removal of the primary tumor is not enough in the treatment of even non-invasive. In addition to endoscopic removal of the superficial tumors, measures against the intraluminal seeding of the cancer cells and their ability to divide should be taken, perhaps in form of routine intravesical therapy of superficial bladder cancer. Several clinical studies revealed that therapy with adjuvant intravesical chemotherapy reduces the risk of tumor recurrence but has no effect on the risk of progression [38]. This clinical observation is in complete agreement with seeding notion. In addition to chemotherapy, Immunotherapy with live BCG vaccine turned to be an effective treatment of carcinoma *in situ* as long ago as 1976 [4], and the vaccine is still the only intravesical agent capable to reduce both of these risks in spite to its complication [4].

That intraluminal shedding and implantation of tumor cells is the mechanism responsible for both synchronous and metachronous multifocal bladder cancer may be of considerable relevance for therapeutic strategies. Additional measures should be directed toward stopping tumor cell seeding and the ability of already implanted tumor cells to divide and growth. This implies more emphasis on intravesical adjuvant therapy in superficial bladder cancer, including the use of anti-inflammatory drugs, antagonists of cell adhesion, and intravesical chemotherapy or immunotherapy with BCG. The possibility of seeding viable cancer cells during the endoscopic removal of the tumor suggest the avoidance of unnecessary trauma to the urethelium during this procedure also seems stronger. The practice of taking random bladder biopsies or removing a benign prostate at the time of bladder tumor surgery seems illogical in this perspective and should probably be avoided.

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