ELSEVIER

Urologic Oncology: Seminars and Original Investigations 32 (2014) 28.e11–28.e20

UROLOGIC ONCOLOGY

Review article

Molecular aspects of upper tract urothelial carcinoma

Nilay Patel, M.D., F.R.C.S.[a,*], Manit Arya, M.D., F.R.C.S.[b], Asif Muneer, M.D., F.R.C.S.[b], Tom Powles, M.D., M.R.C.P.[c], Mark Sullivan, M.D., F.R.C.S.[a], John Hines, F.R.C.S.[b], John Kelly, M.D., F.R.C.S.[b]

[a] *Department of Urology, Churchill Hospital, Oxford, UK*
[b] *Department of Urology, University College Hospital, London, UK*
[c] *Barts Cancer Institute, Barts and The London School of Medicine and Dentistry, London, UK*

Received 23 July 2012; received in revised form 1 October 2012; accepted 3 October 2012

Abstract

Objectives: Primary upper tract urothelial carcinoma (UTUC) is a relatively rare tumor with up to 60% of cases being muscle invasive at presentation. In this article we review the molecular biology of UTUC, an understanding of which may help to address some of the dilemmas surrounding the diagnosis and treatment of this disease and ultimately lead to the introduction of personalized treatment plans.

Methods: The literature search on the molecular aspects of UTUC was performed using the National Library of Medicine database.

Results: UTUC and urothelial carcinomas of the bladder share many common biological pathways. UTUC are more commonly associated with conditions such as Balkan Endemic Nephropathy and Hereditary Non Polyposis Colon Cancer (HNPCC), the molecular basis of which is now being understood. A large number of potential biomarkers have been studied to help identify robust prognostic markers in UTUC.

Conclusion: Advances in our understanding of the biology of UTUC is may in the future help to identify novel druggable targets, clinically applicable biomarkers and guide treatment of the rare but lethal condition.

Keywords: Urothelial carcinoma; Upper tract; Transitional; Molecular; Cancer; Genetics

1. Review

1.1. Search strategy and selection criteria

A literature search on the molecular aspects of upper tract urothelial carcinoma (UTUC) was performed using the National Library of Medicine database. A MEDLINE search was performed using combinations of the following terms: urothelial carcinomas, upper urinary tract, primary, carcinoma, transitional cell, molecular biology, risk factors, DNA repair, genes, genetics, methylation, micro RNA, microsatellite instability, carcinogen, prognosis, mutation, biomarker, tumor suppressor, chemotherapy, nephroureterectomy, adjuvant treatment, and neoadjuvant treatment.

2. Introduction

Primary UTUCs are relatively rare tumors, with an estimated incidence of 1 to 2 cases per 100,000 individuals

Abbreviations: UTUC, upper tract urothelial carcinoma; UCB, urothelial carcinoma of the bladder; TNM, tumor, nodes, metastasis; BEN, Balkan endemic nephropathy; CHN, Chinese herb nephropathy; AA, aristolochic acid; DNA, deoxyribose nucleic acid; HNPCC, hereditary non-polyposis colorectal cancer; MMR, mismatch repair; PCR, polymerase chain reaction; MSI, microsatellite instability; DSS, disease-specific survival; OS, overall survival; DFS, disease-free survival; MFS, metastasis-free survival; RFS, recurrence-free survival; PFS, progression-free survival; mRNA, messenger ribose nucleic acid; TKI, tyrosine kinase inhibitor; EMT, epithelial to mesenchymal transition.

* Corresponding author. Tel.: +44 1865 741841; fax: +44 1865 226086.
E-mail addresses: nilay.patel@ouh.nhs.uk (N. Patel), manit_arya@hotmail.com (M. Arya), mramuneer@gmail.com (A. Muneer), Thomas.Powles@bartsandthelondon.nhs.uk (T. Powles), mark.sullivan@ouh.nhs.uk (M. Sullivan), johnhinesurology@aol.com (J. Hines), j.d.kelly@ucl.ac.uk (J. Kelly).

1078-1439/$ – see front matter
http://dx.doi.org/10.1016/j.urolonc.2012.10.002

per year [1]. UTUCs comprise urothelial carcinomas originating anywhere, from the renal calyces to the ureteric orifices. Tumors arising from within the renal pelvis occur 4 times more commonly than ureteric lesions. In comparison to urothelial carcinoma of the bladder (UCB), primary UTUCs are less common, representing only 5% of all urothelial cancers and less than 10% of renal tumors.

Radical nephroureterectomy with excision of an ipsilateral bladder cuff is the gold standard treatment for organ-confined UTUC [1]. There are conflicting reports regarding oncological outcomes between tumors in the renal pelvis and ureteric tumors. A multi-national multi-centre study by Raman et al. reported no difference in outcomes between these 2 groups; however, a multi-centre study from France observed that ureteric tumors had a poorer prognosis [2,3]. At present, both tumor types are grouped together in the tumor, nodes, metastasis (TNM) classification system as UTUC. The UTUC Collaboration demonstrated that radical nephroureterectomy resulted in all stage 5-year recurrence-free rates of 69%, and cancer-specific survival of up to 73% [4]. Some patients with low-risk disease may be suitable for a more conservative approach with endoscopic ablation or segmental resections.

Comparative stage specific oncologic outcomes for UCB managed with radical cystectomy and UTUC managed with a radical nephroureterectomy have recently been reported [5]. Non–muscle invasive UCB was associated with higher recurrence rates and mortality compared to non–muscle invasive renal pelvicalyceal tumors. No difference in outcomes was observed between UCB and UTUC for prmary tumor stage 2 (pT2) and pT3 tumors; however, pT4 tumors in patients with UTUC were associated with higher recurrence rates and poorer cancer-specific mortality rates compared to UCB.

The prognosis for patients with locally advanced or node-positive disease is poor, with a median survival of between 6 and 26 months [4]. Muscle-invasive UCB has been shown to be sensitive to multi-agent platinum-based chemotherapy; unfortunately, neither neoadjuvant nor adjuvant chemotherapy appear to offer any significant clinical benefit for high risk or advanced UTUC. A retrospective multi-centre study by Hellenthal et al. reported no significant difference in overall or cancer-specific survival between patients who did and did not receive adjuvant chemotherapy [6].

The study of the molecular basis of primary UTUC over the past 2 decades has greatly increased our understanding of the biology of this disease. The identification of oncogenic pathways and validated biomarkers may in the future help to improve the management of UTUC.

3. Etiology

Exposure to numerous environmental factors is associated with the development of UTUC. The risks associated with exposure to tobacco and aromatic amines such as benzidine and β-naphthalene are common to UCB and UTUC [7].

Balkan endemic nephropathy (BEN) is a renal disease affecting parts of Bosnia, Bulgaria, Croatia, Romania, and Serbia, that is characterized by chronic renal failure, tubulointerstitial fibrosis and UTUC. The incidence of UTUC in these regions is 60 to 100 times greater than the rest of the world. The biological characteristics of UTUC within these regions differs from the norm, as tumors are more commonly bilateral, do not show a male preponderance, and occur 10 years after a diagnosis of BEN. A similar association was described in Belgium, where patients developed renal failure after taking Chinese herbal products. Many of these patients later went on to develop UTUC, with histological features similar to those of BEN-induced UTUC [8].

Recent studies have implicated the plant extract aristolochic acid (AA), a nitrophenanthrene carboxylic acid derived from the plant species Aristolochia, as the causative agent responsible for the development of Chinese herb nephropathy (CHN) and BEN. AA undergoes metabolic activation to generate the ultimate carcinogen, aristolactam-nitrium ion, which binds to DNA, forming DNA adducts that cause T→A transversions in codon 139 of exon 5 in the p53 gene [9]. This particular p53 mutation is common in patients with CHN and BEN who develop UTUC, but is rare in the normal population [10].

Not all individuals with CHN and BEN exposed to AA develop renal failure or UTUC. Variability in the expression and activity of enzymes activating and detoxifying AA account for this variability in disease progression. Polymorphisms of the cellular nitroreductase NQO1 have been found to predispose patients suffering from BEN to the development of primary UTUC [11].

An individual's susceptibility to developing UTUC is determined by his/her ability to counteract carcinogens. Sulfation by the cytosolic sulfotransferase enzyme family is one of the processes by which environmental carcinogens are detoxified. A functional polymorphism in the SULT1A1 gene occurs frequently in UTUC, the resulting SULT1A1*2 variant has decreased carcinogen detoxification rates [12].

4. Genetic instability in UTUC

A variety of techniques have been used to identify the chromosomal aberrations that are associated with the development of UTUC. Of the multitude of chromosomes that demonstrate alterations, losses in 9q are present in 50% of the cases, suggesting a decisive role for chromosome 9 in the initiation and development of UTUC [13]. It has been suggested that chromosome 9 harbors at least 5 candidate regions for tumor suppressor genes involved in human urothelial neoplasia; 9p22p23, 9p11p13, 9q12～q13, 9q21～q22, and 9q34 [14]. Primary UTUCs share many of the genetic changes identified in UCB. Rigola et al. demonstrated a close concordance between UTUC and UCB with respect to losses at 2q, 8p, 9q, 11p, 13q, 17p, and 18q, and gains at 1q, 6p, 8q, and 17q [13]. Wu et al. suggested that alterations in chromosomes 7, 15, and 19 may be