Solid Tumour Section

Review

Bladder: Urothelial carcinomas

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Identity


Classification

Histologic types:
- Urothelial carcinoma of the bladder, herein described,
- Squamous cell carcinoma,
- Adenocarcinoma (2%), rare,
- Poorly differentiated carcinoma/small cell carcinoma, exceptional.

Clinics and pathology

Disease
Cancer of the urothelium.

Epidemiology
Urothelial carcinoma of the transitional epithelium is the most frequent bladder cancer in Europe and in the USA, representing 90-95 % of cases, while
squamous cell carcinoma represents only 5% in these countries, but up to 70-80% of cases in the Middle East; annual incidence: $250/10^6$, 2% of cancers, the fourth cancer in males, the seventh in females, 3M/1F; occurs mainly in the 6th-8th decades of life; risk factors: cigarette smoking and occupational exposure (aniline, benzidine, naphtylamine); 20 to 30 yrs latency after exposure.

**Clinics**
Hematuria, irritation.

**Pathology**
Grading and staging: tumours are:
- graded by the degree of cellular atypia (G1->G3), and staged:
  - Papilloma,
  - Papillary tumor of low malignant potential (PTLMP),
  - Papillary urothelial carcinomas low grade,
  - Papillary urothelial carcinomas high grade.

**Treatment**
Resection (more or less extensive: electrofulguration -- > cystectomy); chemo and/or radiotherapy, BCG-therapy.

**Evolution**
Recurrence is highly frequent.

**Prognosis**
According to the stage and the grade; pTa is of good prognosis (> 90% are cured); prognosis is uncertain in pT1 and G2 tumours. 20% survival at 1 yr (stable at 3 yrs) is found in T4 cases; however, identification of individual patient's prognosis is often difficult, although of major concern for treatment decision and for follow up.

Multiple endpoints may be identified in bladder cancer. Recurrence (does it come back), recurrence rate (how soon/often does it come back), progression and (disease specific) survival are of importance. Patients with superficial bladder cancer (pTa and pTis) are frequently evaluated by cystoscopy to allow early detection of a possible recurrence and to prevent disease progression to invasive, potentially lethal, bladder cancer.

According to mutational status of FGFR3 and TP53; tumors with an FGFR3 mutation have a lower recurrence rate, tumors with elevated immunohistochemical expression of p53 and MIB-1 have the highest recurrence rate; and the highest propensity for progression and death of disease (see figure below).

**Cytogenetics**

**Cytogenetics Morphological**

**Karyotype**
Urothelial carcinomas exhibit pseudo diploid karyotypes with only a few anomalies in early stages, evolving towards pseudo-tetraploides complexes karyotypes. Partial or complete monosomy 9 (-9) is an early event, found in half cases. Deletion (11p) or -11 is found in 20-50% of cases, more often in high grade and invasive tumours. Del(13q) is found in 25% of cases and correlated with high grade/stage; tumours with Rb alterations are invasive. Del(17p) is a late event, found in 40% of cases; TP53 alterations are correlated with grade and stage, tumour progression, and a worse prognosis. Del(1p), i(5q), +7, and many other rearrangements - more often deletions than duplications - are frequently found. These losses of heterozygocity point to a multistep complex process involving tumour suppressor genes.

**Amplifications**
Chromosome 1: P73 (1p36) is often over-expressed. Chromosome 8: C-MYC (8q24) is rarely amplified.
Chromosome 11: cyclin D1 is often over-expressed. Amplifications 10q13-14, 13q21-31 and 17q22-23 have been noted.

**Losses**

Chromosome 8: loss of 8p12-22. The potential target is the FEZ1/LZTS1 gene, which is downregulated in high-grade carcinomas.

Chromosome 9: Allelic loss on chromosome 9q is a very frequent event in bladder carcinogenesis. Monosomy 9 or deletions of chromosome 9 are found in about 50% of cases; at times found as the sole anomaly, demonstrating that it is an early event, found equally in pT1a stage and in more advanced stages; not associated with a given grade, and not correlated with p53 expression. Efforts have been directed towards identifying the postulated tumour suppressor genes on this chromosome arm by deletion mapping and mutation analysis. However, no convincing candidate genes have been identified. Homozygous deletions of CDKN2A/MTS1/P16 (9p21) have been documented; LOH + mutation on the second allele of CDKN2A are rare, but of significance; CDKN2A is implicated in pTa stage but not in pTIS, where p53 is found mutated; CDKN2B/INK4B/P15 (9p21) is also implicated in a small subset of cases. LOH + mutation on the second allele of TSC1 (9q33-34) has been described. Homozygous deletion and methylational silencing of a candidate gene DBCCR1 (9q32-33) has been reported. Chromosome 10: PTEN (10q23), appears to be implicated in a very few percentage of cases (homozygote deletion has been found); Fas/APO1/CD95 (10q24): loss of one allele and mutation in the second allele has been reported; a hot-spot of mutations has been determined. Chromosome 11: HRAS1 (11p15.5) is mutated in 15% of cases.

Chromosome 13: an altered Rb (13q14) is expressed in 30 to 40% of tumours; these are high stage, invasive, and indicate a short survival; 90% of tumours expressing Rb are invasives; disregulation of the normal P16-Rb interactions have been documented, with hyper expression of Rb and loss of function of P16.

Chromosome 17: P53 (17p13) alterations are correlated with grade and stage (often PT3), and tumour progression; P53 is mutated in more than 50% of high grade/stage tumours, and in most PTIS; P53 is a prognostic factor: by high grade/stage tumours, those expressing P53 are of a worse prognosis; by low grade/stage, those not expressing P53 are of better outcome; there is usually LOH + mutation on the second allele of P53; ERBB2 (HER2/Neu) (17q21) is expressed in high grade/stages tumours, in metastases, and is associated with relapses; NF1 (17q11) expression may be very low in tumours.

**LOH**

LOH analysis in bladder cancer has so far not led to the identification of tumor suppressor genes. LOH appears to be numerous within a given chromosome (e.g. on chromosome 9 five regions, 9p21, 9q22, 9q31-32, 9q33 and 9q34, and on chromosome 5 four regions, 5q13.3-q22, 5q22-q31.11, 5q31.1-q32, and 5q34, and on chromosome 3 frequent LOH has been found in three regions, 3p12-14, 3p21.3-22 and 3p24.2-25), but loci remain to be precised, as reports are controversial. Due to the unique possibility to study multiple recurrent tumors from the same patient, it is now becoming apparent that loss of heterozygosity (LOH) on chromosome 9 is almost never the characteristic first step in tumor development. LOH can be detected in up to 67% of markers tested. The regions of loss are multiple and variable in different tumours from the same patient and expand in subsequent tumours. Moreover, the regions of loss on chromosome 9 vary from patient to patient. To explain the type and extent of genetic damage in combination with the low stage and grade of these tumors, it was hypothesized that in bladder cancer pathogenesis an increased rate of mitotic recombination is acquired early in the tumorigenic process.

**Cytogenetics Molecular**

(Matrix) CGH

Array-based comparative genomic hybridization detected high-level amplification of 6p22.3 (E2F3), 8p12 (FGFR1), 8q22.2 (CMYC), 11q13 (CCND1, EMS1, INT2), and 19q13.1 (CCNE) and homozygous deletion of 6p22 (TRAF6), 9p21.3 (CDKN2A/p16) and 8p23.1.

**Genes involved and proteins**

**FGFR3**

**Note**

The expression of a constitutively activated FGFR3 in a large proportion of bladder cancers is the first evidence of an oncogenic role for FGFR3 in these carcinomas. FGFR3 currently appears to be the most frequently mutated oncogene in bladder cancer: it is mutated in more than 30% of cases. FGFR3 seems to mediate opposite signals, acting as a negative regulator of growth in bone and as an oncogene in several tumour types. Complete elucidation of the role of FGFR3 in normal and malignant tissues requires further investigation. Missense mutations were observed identical to those in thanatophoric dysplasia (R248C, S249C, G372C, and K652E), achondroplasia and SADDAN (G380/382R and K650/652M, respectively) and Crouzon Syndrome with Acanthosis Nigricans (A393E). Furthermore, a K650/652T mutation was found not previously identified in carcinomas or
thanatophoric dysplasia. In urothelial papilloma, generally considered a benign lesion, 9/12 (75%) mutations were found. Another novel finding was the occurrence of two simultaneous FGFR3 mutations in four tumours.

**TP53**

**Note**

The TP53 gene in bladder cancer is mainly an indicator of progression and recurrence rate. Interestingly, mutations in FGFR3 and TP53 are mutually exclusive in bladder cancer.

**HRAS**

**Note**

HRAS mutations are found in approximately 15% of cases.

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