Prognostic Factors of Urological Malignancies

Essay

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وأنزل الله عليك
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وعلَّمَكَ مَا لَمْ تَكُن
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✍ *Mohammed Fathi Abd Allah*

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List of Abbreviations

ASAP : Atypical small acinar proliferation

CAIX : Carbonic anhydrase isoenzyme

CIS : Carcinoma in situ

ECOG : Eastern Cooperative Oncology Group

HGPIN : High-grade PIN

IGCNU : Intratubular germ cell neoplasia, unclassified type

MSKCC : Memorial Sloane Kettering Cancer Centre

PCa : Cancer of the prostate

PSA : Prostate-specific antigen

PUNLMP : Papillary urothelial neoplasms of low malignant potential

TNM : Tumour Node, Metastasis

UCLA : University of California Los Angeles

UICC : Union Internationale Contre le Cancer

WHO : World Health Organization

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Introduction

It is very important that relatively indolent tumors can be distinguished from potentially lethal tumors; therefore, prognostic factors are necessary. The term prognosis for patients with established any cancer can be defined as the prediction of future behavior of the tumor, either in the absence or after application of therapy. With the assessment of prognostic factors, attempts are being made to predict the clinical course of the disease in a specific patient. A prognostic factor can be defined as a qualitative or quantitative alteration or deviation from normal of a molecule, substance or process that can be detected by some kind of assay and that is correlated with prognosis ***(Hayes et al., 1996).***

Renal cell carcinoma, which accounts for 2% to 3% of all adult malignant neoplasms, is the most lethal of the urologic cancers. Traditionally, more than 40% of patients with RCC have died of their cancer, in contrast with the 20% mortality rates associated with prostate and bladder carcinomas ***(Pantuck et al., 2001).*** Prognostic factors can be classified as tumor, patient, and treatment- related factors. The key factors include performance status, tumor stage, histological type, and grade ***(Lang and Jacqmin, 2003).*** Several biochemical and molecular markers have been proposed including p53, CD-44, G250/ CAIX and others ***(Bui, et al., 2003).***

Urothelial tumors of the renal pelvis account for approximately 10% of all renal tumors and 5% of all urothelial, Upper tract urothelial tumors occur more frequently in men than in women and also occur more frequently in white people as compared to black people, with a white-to-black ratio of 2 : 1 ***(Greenlee et al., 2000).*** The significant prognostic factors for survival rates are the T stage, grade, multiplicity, location, lympho-vascular invasion, and surgical modality ***(Matsui et al., 2005).***

Bladder cancer is the fourth most common solid tumour in men and the eighth most common in women, ranking seventh and tenth, respectively, among causes of cancer death ***(Jemal et al., 2002).*** The most useful prognostic parameters for tumor recurrence and subsequent cancer progression in the patient with superficial tumors are tumor grade, depth of tumor penetration (stage), lymphatic invasion, tumor size, urothelial dysplasia or carcinoma in situ in neighboring or distant urothelial areas, papillary or solid tumor architecture, multifocality, and frequency of prior tumor recurrences, the most important of these are grade, stage, and presence of carcinoma in situ ***(Millan-Rodriquez et al., 2000).***

Worldwide more than half a million men are diagnosed with prostate cancer annually, accounting for a tenth of all new male cancers. It is the third most common cancer in men after lung and stomach ***(Ferlay et al., 2000).*** The primary guides in prognosis are the anatomical extent or stage of the disease, Tumour Node, Metastasis (TNM) classification ***(Sobin and Wittekind 2002),*** however the most relevant are PSA and Gleason

score and the post radical prostatectomy margin status is also a very strong independent prognostic factor ***(D'Amicoetal, 2003).***

Cancer of the penis is a rare malignancy with incidence rates of 0.3 to 8 per 100, 000 ***(Misra et al., 2004).*** Factors predisposing to local recurrence after treatment are increasing T stage and increased grade of differentiation (Horenblas S, et al. 1992.). The most important prognostic factor for survival is the prescence or absence of lymph node metastasis.

Primary urethral cancer is extremely rare, accounting for less than 1% of all malignancies. Female urethral cancer is four times more common than male urethral cancer. It typically presents after the age of 60. Primary carcinoma of the urethra accounts for only 0.02% of all malignancies in females ***(Dalbagni et al., 1998).*** The prognosis depends on the cancer's anatomical location and depth of invasion. Tumor stage clearly is an important prognostic indicator, with advanced tumors having poor prognosis ***(Eng et al., 2003).***

Testicular cancer represents between 1% and 1.5% of male neoplasms and 5% of urological tumours in general ***(La Vecchia et al., 2009).*** The prognosis depends on the anatomical extent of disease, assessment of serum tumour markers, including nadir values of HCG, AFP and LDH after orchidectomy (S category), clear definition of regional nodesand some N-category modifications related to node size ***(Sobin et al., 2009).***

Neuroblastoma accounts for 8% to 10% of all childhood tumors and is the most common malignant tumor of infancy ***(Young et al., 1986).*** The most important prognostic factors are age and origin of the tumor.Hyperdiploid tumor DNA is associated with a favorable prognosis ***(Ladenstein et al., 1998).*** while N-*myc* amplification is associated with a poor prognosis regardless of patient age ***(Tonini et al., 1997).*** Elevated serum ferritin, elevated serum lactate dehydrogenase and the presence of neuroblastoma cells in bone marrow during or after chemotherapy are each associated with poor prognosis ***(Seeger et al., 2000).***

Wilms' tumor typically affects young children (median age, 3.5 years), with more than 80% of cases occurring in those younger than 5 years. Nevertheless, older children and occasionally even adults can be affected ***(Kalakapural et al., 2004).*** Determination of the prognostic factors is very important to predict outcomes. These factors are tumor size, histology, and lymph node metastases and telomerase ***(Dome et al., 2005).***

Aim of the Work

Is to spotlight the role of various prognostic factors in management and follow up of genitourinary tumors.

Chapter (1):
Tumour Biology

Cancer susceptibility is driven primarily by six types of genes:

1. ***Oncogenes:*** A series of over 60 genes have been identified that are activated or overexpressed and that have a positive effect in the induction of growth.These constitutive genes have a prefix like c-*myc*. If they are mutated and inserted by viruses this prefix changes to v, like v *src*.

2. ***Suppressor genes:*** Loss of the function of a suppressor gene essentially removes a brake on cell growth, thus permitting it to become up-regulated (examples are p53, Rb, and p16).

3. ***DNA repair genes:*** Normal or induced errors in DNA copying, DNA damage from the environment, or oxidative damage must be corrected or the gene will be mutated or silenced. In colon cancer, a group of mismatch repair genes (MSH2, MLH1, PMS1, and PMS2) have all been shown to be inherited and to induce cancer by accumulation of DNA damage. We know little about how telomere damage is repaired or how repetitive DNA transposons are regulated.

4. ***DNA defense genes:*** These genes protect the DNA from oxidative damage or electrophiles that can form adducts to the bases that are detrimental. There are enzymes that protect the cell against ROS that form free radicals and produce oxidative damage to the cell. As the mitochondria carry out their aerobic oxidation, 4 electrons are required to reduce molecular oxygen to water.

5. ***Viral genes:*** Retroviruses, polyoma, adenoma, andvT-antigen, E1, E6, and oncogenes.

6. ***DNA methylation genes:*** DNA methylation is altered in many cancers and for unknown reasons. Hypermethylation of CpG islands in promoter regions can silence genes. DNA methylation can vary in maternal and paternal genes, termed imprinting. Loss of imprinting (LOI) is a common change in cancers.

(Marzo et al., 2003)

At present, all of the above six mechanisms are being studied to determine what causes urologic cancers. At the moment, there is only definitive evidence that the VHL gene is associated with von Hippel-Lindau syndrome, and the WT1 gene isvassociated with Wilms' tumor. The p53 gene is associated with bladder cancer but it may only be a progression marker, as it is in prostate cancer.How do the aforementioned oncogenes and suppressor genes function within the cell to cause cancer? They appear to regulate cell replication, death, and growth. There are about 60 oncogenes of primarily four types:

1. Genes for growth factors or their receptors (e.g., platelet-derived growth factor [PDGF], *erb*-B, and RET).
2. Genes affecting cell-signaling pathways, such as *ras* and *src*.
3. Genes acting as transcription factors that activate early growth genes, such as the *myc* oncogenes.
4. Genes affecting the cell cycle: Bcl-2 is an inhibitor of cell death that when overexpressed, blocks apoptosis and allows

cells to survive and accumulate. Overexpressing factors that bind to suppressors can remove the brake. For example, MDM-2 removes the suppressor brake p53 by binding to it and inactivating it. Many virus proteins are expressed in an infected cell, such as large T, E1A, and E7, and have the ability to complex suppressor molecules, such as p53 and Rb. In summary, turning these genes on turns on cell growth. Suppressors are brake molecules that turn growth off. Removing the brake, of course, turns on the growth. These brakes can be removed either by inheriting the loss of this gene, by mutating the gene and activating it, or by turning of the gene through regulation, which is the case when the DNA in its promoter region is methylated.

(Marzo et al., 2003).

How do the suppressor genes function as brakes? Many of these genes are located in the nucleus and affect the cell cycle regulation. The Rb gene is present in all cells and codes for a master brake on the cell cycle that is discussed in the following. The p53 is one of the bestknown suppressors and is abnormally regulated in most cancers. It blocks the cell cycle by inducing a series of cell cycle kinase inhibitors. This p53 protein is activated when the cell detects damage, such as DNA breakage, and blocks the cell cycle at the G1/S checkpoint to allow time for DNA repair. If the damage is extensive the p53 induces abnormal cells to undergo a suicide through apoptosis. The p53 can also affect the mechanism of mitosis; abnormalities may result in mitotic dysjunction MTS-1, also called p16, is another suppressor