

Solid Tumour Section

Mini Review

Head and neck squamous cell carcinoma

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Clinics and pathology

Disease

Head and neck cancer as defined here includes the squamous cell carcinomas of the oral cavity, pharynx and larynx. This malignancy is an important public health problem worldwide with more than 500000 new cases diagnosed each year. Patients often present with advanced stage disease and despite combined therapy outcome remains poor. For early stage, patients can be at high risk for second primary when cured of their initial cancer which poses the main threat to survival.

Etiology

The major risk factor for head and neck cancer is chronic exposure of epithelia to tobacco smoke and alcohol. Environmental factors such as wood and cement dusts as well as human papilloma virus type 16 and 18 (HPV) infection have been related to an increased risk of developing head and neck squamous cell carcinoma (HNSCC). Recent studies confirm that oropharyngeal tumors are often HPV-positive and compose a distinct clinical and pathological entity with less TP53 mutations and better prognosis as compared to HPV negative tumors. Epstein Barr Virus infection is related to nasopharyngeal SCC in south china and oral cavity tumors are frequent in betel chewers.

Epidemiology

Both hereditary and environmental factors are implicated in head and neck carcinogenesis and their roles are difficult to separate. Several cancer prone syndromes are associated with a increased risk of head and neck cancer, including Lynch-II, Bloom syndrome, Fanconi anemia, ataxia telangiectasia and Li-fraumeni syndrome. But genetic susceptibility to head and neck cancer is more likely to be due to various degrees of DNA maintenance after exposure to tobacco carcinogens. Mutagen sensitivity tests, polymorphism

in DNA repair enzymes or in carcinogens metabolizing enzymes supports the role of heredity in HNSCC. Among the polymorphism tested, GSTM1 and GSTT1 null phenotypes are associated with an increased risk of HNSCC. Concerning XRCC1, the Arg allele (Arg194Trp) and the Gln allele (Arg399Gln) are also linked to an increased risk of oral and pharyngeal cancers.

Pathology

Head and neck cancer are usually diagnosed in men after 50, patients can present with one or more distinct localization (10-15% at diagnosis) and 25% will develop a second cancer within 5 years from diagnosis. Cancer can develop from leucoplakia, erythroplakia or apparently normal epithelium. Premalignant lesions showing abnormal DNA content are at high risk of transformation. Clinical prognosis factors counts, tumor size, node involvement and smoking habits. Tumor markers related to prognosis counts EGFR expression, cyclin D1 or cyclin E expression, serum soluble IL-2 receptor concentrations and loss of chromosome arm 18q.

Treatment

First goal is locoregional control achieved by surgery or radiotherapy. For high staged tumors combined surgery+/-radiotherapy+/-chemotherapy can be used. New treatment strategies are in development. Adenovirus have been developed that restore TP53 or P16 activity or that selectively replicates in TP53 deficient cells. Agents that inhibit signal transduction as tyrosine kinase inhibitors are also under evaluation in HNSCC specially those targeting the EGF receptor.

Cytogenetics

Note

Chromosomal abnormalities are very frequent in head and neck tumors leading to very complex karyotypes

with more than 70% of tumors being aneuploid. Although most chromosome arms can be targeted by loss or gain of fragments, cytogenetic studies, Comparative Genome Hybridization (CGH) studies and molecular genetics studies demonstrated the existence of recurrent alterations some of which are found early in carcinogenesis. Loss of chromosome arm 3p and/or 9p is found in over 80% of tumors, loss of 17p involves more than 50% of the cases these alterations are associated with early tumor development. Losses of 5q, 8p, 4q 10q or 13q are found in nearly 30% of tumors and loss of 11p in less than 20% these alterations are preferentially associated with tumor progression. Concerning fragments gain, amplification at 11q and 3q clearly participate in head and neck carcinogenesis and concern nearly 70% of the cases. 3q amplification is seen in early tumor development. Studies showed that patterns of chromosomal alterations can be associated with clinical parameters such as deletions at 10q25-q26 and 11p13-p14 that are significant for metastasizing carcinoma and amplification of 11q could be a bad prognosis factor.

Tumor proliferation is known to result from activation of growth promoting pathways and inhibition of growth downregulation pathways. Several chromosomal segments involved in head and neck carcinogenesis harbor genes implicated in growth regulation.

Tumor suppressor genes

- Chromosome arm 3p: At least three regions have been identified at 3p 3p13-3p21, 3p21.3-3p23, 3p25. Four genes have been studied for the presence of inactivating mutations VHL, TGFBR2, FHIT and OGG1. Very few mutations have been found in TGFBR2 and only abnormal transcripts were detected for FHIT leading to the conclusion that it is still unclear whether or not these genes are the targets of 3p deletions.

- Chromosome arm 9p: CDKN2A (P16) is a cell cycle regulatory gene located at 9p that is down regulated in HNSCC through homozygous deletion or promoter hypermethylation.

- Chromosome arm 17p: TP53 is mutated in over 60% of HNSCC there is a good correlation between mutation and LOH at 17p. In HNSCC 50% of TP53 mutations are nonsense, deletions, insertions or splice site junctions mutations and 50% are missenses. It has been clearly demonstrated that smoke carcinogens have a causal role in the formation of TP53 mutations and that the prevalence is greater in heavy smoker patients. TP53 mutations could be an indicator of a bad response to neoadjuvant chemotherapy in HNSCC

- Chromosome arm 18q: Loss of 18q is linked to bad prognosis in HNSCC. Genes SMAD2, SMAD4 and DCC do not seem to be the right targets. The delineation of a common region of loss at 18q22 did not allow the identification of a new tumor suppressor gene.

- Chromosome arm 13q: No mutation in RB were identified in HNSCC.

- Chromosome arm 10q: No mutation in PTEN were identified in HNSCC.

Oncogenes

- Chromosome band 11q13: EMS1, FGF3, FGF4 et CCND1 are amplified in HNSCC.

- Chromosome arm 3q: The PIK3CA gene but not p63 is likely to be the target of 3q26-qter gain.

- The Wnt, APC, bcatenin pathway: No mutation in the bcatenin gene in HNSCC.

- MAP kinase pathway: The only head and neck tumors with constitutive RAS activation are from Indian and Taiwanese patients that can harbor HRAS or KRAS mutation.

- Epigenetic alteration in HNSCC: Genes can be inactivated by promoter hypermethylation, in head and neck cancer the phenomenon has been demonstrated for several genes including P16, MGMT and DAP-kinase. DAP-kinase is implicated in INFG mediated apoptosis and DAP-kinase promoter hypermethylation is related to advance stage tumors.

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