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Impact of Molecular Markers in Head and Neck Squamous Cell Carcinomas

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About the Study

Squamous Cell Carcinomas (SCC) of the lip and oral cavity are among the most frequently diagnosed cancers in South Central Asia due to widespread habit of betel nut chewing. Alcohol and tobacco consumption and ultraviolet light exposure have also made this a common diagnosis in eastern and Western Europe and Australia/ New Zealand [1].

Treatment of oral cavity SCC are multidisciplinary and depend on stage of disease and patient related factors like age, performance status, patient choice and presence of comorbidities. Early-stage patients are treated with surgery or tele therapy/brachytherapy alone, whereas advanced staged diseases need surgery followed by radiotherapy with or without chemotherapy or chemo radiotherapy upfront. Inoperable diseases are treated with radiotherapy generally with concurrent chemotherapy or palliative / best supportive care depending on performance status of patient [2].

Matter of concern

Head and Neck Squamous Cell Carcinomas (HNSCC) are aggressive in nature known for recurrence in up to 50% of patients [3]. Recurrences may be attributed to patient lifestyle related factors like tobacco and alcohol consumption, genetic and pathological components and suboptimal treatment. Recurrent tumors may be treated with salvage surgery, reradiation or palliative intent radiotherapy/best supportive care depending on various factors like tumor location, time since previous treatment and performance status of patient.

HNSCC are heterogeneous groups of disorders that respond variably to treatment modalities like radiotherapy and chemotherapy and differ in prognosis. In addition to stage of disease, HPV status, depth of invasion, lymphovascular spread, patterns of invasion, perineural invasion, extra nodal extension, margin status after surgery patient's age, nutritional status, performance status, addiction history also determine not only the treatment offered to a patient but also the disease response to treatment. Heterogeneity in behaviour of HNSCC can possibly be attributed to molecular pathologies underlying development of HNSCC and molecular response to treatment modalities.

Analysis of the status of the problem

Several studies over the last few years have identified markers associated with a poorer prognosis in HNSCC [4]. Tissue biomarkers like HPV, P53, and EGFR status and their association with treatment related outcomes has been the subject of several research projects.

The tissue samples of 290 HNSCC patients treated with chemotherapy and radiotherapy were subject to Immunohistochemistry (IHC) evaluation for Cyclin D1, EGFR and p53 biomarkers and the results were evaluated against post radiotherapy tumor evaluation by clinical and radiological investigations. Resistance to chemoradiation and increased risk of local and distant recurrence was seen in tumors over expressing Cyclin D1, EGFR and p53 [5].

The AKT1, AKT2, and AKT3 kinases have emerged as critical mediators of signal transduction pathways downstream of activated tyrosine kinases and phosphatidylinositol 3-kinase. Activation of the PI3K/Akt pathway is associated with tumor genesis and resistance to apoptosis and ionizing radiation [6]. Activated AKT/mTOR signaling is associated with carcinogenesis and chemoresistance, thus making it a potential therapeutic target [7,8]. PI3K is involved in cell survival, migration and proliferation and mutations in this pathway arise in 30.5% of HNSCC [9]. Role of drugs like Bimiralisib, Everolimus, Rapamycin,Temsirolimus, etc which target these pathways are being investigated in advanced/recurrent/metastatic HNSCC.

Linge et al. identified association between MET and SLC3a2 increased distant metastases and decreased overall survival in HNSCC treated with surgery and chemoradiotherapy [10]. High expression of ALDH1 and SOX2 correlated with lymph node metastasis, high tumor grade and poor prognosis in a study by Michifuri et al. [11]. A study by Mannelli et al. linked the role of proliferating cancer stem cells in tumor progression in patients of HNSCC with lymph node involvement. Immunohistochemical showed high expression of CD44/CD133 cancer cells, with the highest clonogenic capacity of CD44+ subpopulation [12].

Immunohistochemistry studies have revealed over expression of ALDH1, CD44, OCT4 and SOX2 proteins in tongue SCC which are notorious for their poor response to treatment and recurrences have

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been. Huang et al. associated SOX2 with poor prognosis independent of other factors in these patients [13]. Glucose-regulated Protein 94 (GRP94) is a member of the Hsp 90 family which plays an important role in regulating mitogenesis, cell cycle and apoptosis and its association with radioresistance in oral cavity cancer patients was in a study by Lin et al. where it was also identified as an independent predictor of LRC, DSS and OS [14].

There are several pathways by which tumor cells upregulate PD-L1 expression and it has been seen that CD274 (the gene encoding PD-L1) and CD279 (the gene encoding PD-1) DNA copy numbers were significantly increased in HNSCC [15]. Pembrolizumab and Nivolumab have been recommended for treatment of recurrent/ metastatic non nasopharyngeal cancers. Studies showed better overall survival in patients recurrent/metastatic HNC treated with Nivolumab when PD-L1 expression was high [16,17].

Chemo radiotherapy is the standard management of locally advanced HNSCC in most patients. Thus, genetic pathways involved in development of resistance to chemotherapeutic agents need attention as they will lead to poor Oncological outcomes. Friedrich et al. investigated genes involved in chemotherapeutic resistance in Oral Cavity Squamous Cell Cancers (OCSCC) using reverse transcriptase Polymerase Chain Reaction (PCR). Bcrp (breast cancer-related protein) expression was found to be increased in Stage III and IV OCSCC and correlated with shorter survival periods. Increased expression of mdr1 (p-glycoprotein-mediated multi-drug resistance), mrp1 (multi-drug resistance-related protein) and bcrp was found to be significantly associated with loss of differentiation of tumor cells in these patients [18]. Differential expression of Single Nucleotide Polymorphisms (SNPs) can lead to chemoresistance during treatment [19].

Toxicities during radiotherapy can also be linked to underlying mutations which DNS repair pathways. The XRCC3c.722C>T and Ku70c.-1310C>G polymorphisms were found to be highly associated with dysphagia in after radiotherapy [20]. An association between genetic polymorphisms, XRCC1 c.1196A>G and RAD51 c.-3429 G>C with development of radiation induced mucositis and dysphagia was seen in HNSCC patients [21]. In nasopharyngeal cancer patients, development of subcutaneous fibrosis was higher with wild type alleles of TGFB1 869C and XRCC1 28152A compared to the variant alleles [22]. Severe acute dermatitis was associated with the T allele of RAD51 (3392 G>T) in a metanalysis of head and neck patients undergoing radiotherapy [23].

Advances in management of cancer patients has led to longer survival bringing to the forefront the issue of recurrences and treatment related toxicities which impair quality of life. In this era of personalized medicine and growing awareness of the molecular pathways involved in tumor genesis, treatment response and toxicity development the need for large scale studies to identify these pathways will help customize treatment in the future to maximize patient benefit. Testing for such molecular prognostic and predictive markers should be cost effective, highly sensitive and specific before they can be routinely incorporated into clinical practice.

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