Beyond tobacco in head and neck squamous cell cancers… Emerging era of molecular targeted therapy and virtual biopsy

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common malignancy in the world, with an annual worldwide incidence of over 600,000 cases/year and 350,000 deaths/year.[1,2] Despite advances in cancer therapies, 5-year survival rate for oral cancer has remained relatively constant at approximately 50% over the past three decades.[3,4] This is primarily due to delayed diagnosis, with approximately half of all oral cancers diagnosed at stages III or IV.[5] Historically, HNSCC has been a disease of older males with heavy lifelong tobacco use, high alcohol consumption, poor diet, bad dentition, oral tobacco use, and betel and areca nut chewing, widely prevalent in rural India.[6]

With declining incidence of smoking-related HNSCC, especially in Western countries, newer genetic and viral factors are emerging as determinants of treatment outcome such as human papillomavirus (HPV) status, notably HPV-16, which has emerged as a powerful prognostic indicator, especially in oropharyngeal cancers.[7] HPV-positive patients tend to show favorable prognosis as these patients tend to be younger, healthier, with lower frequency of smoking and alcohol abuse, and also attributable to intrinsic properties of HPV-positive tumor cells, such as increased response to applied therapies, decreased proliferation rate, or an enhanced host immune response toward virus.[8,9]

E6/E7 viral proteins function as dominant oncoproteins of high-risk HPVs inactivating tumor suppressor proteins, p53 and pRb, and modify cell cycle so as to retain differentiating host keratinocyte in a state that is favorable to amplification of viral genome replication.[10] Viral integration appears to be a requirement for carcinogenesis and significant disruption of host genome at the site of viral integration.[11] In contrast to excellent prognosis of HPV-positive oropharynx cancers, HPV-positive oral and nasopharyngeal cancers may carry worse outcome than HPV-negative cancers arising at these subsites.[12] Furthermore, there seems to be an inverse relationship between epidermal growth factor receptor (EGFR) expression and HPV status.

With the identification of common genetic aberrations and altered signaling pathways in HNSCC, treatment of disease is rapidly evolving with the development of new drugs designed to target crucial receptors and signaling pathways involved in carcinogenesis, enabling us to look beyond cisplatin and taxane-based chemotherapy. Genomic gains and losses of smoking-related HNSCC strongly resemble those in squamous cancers of the lung. Genome-wide sequencing and copy number analysis have clarified commonly mutated genes in HNSCC, such as EGFR, fibroblast growth factor receptor (FGFR), hepatocyte growth factor receptor (c-MET), NOTCH1, MLL2, cyclin D1 (CCND1), or phosphoinositide 3-kinase, with mutation frequencies ranging from 18% to 72%.[13] In non-HPV-related HNSCC, continuous tobacco and alcohol exposure can lead to mutational loss of p16INK4A and p53 genes, detected in 80% of HNSCCs and cause uncontrolled cellular growth. For patients with oral SCC (OSCC), high p16INK4A and low EGFR were associated with improved outcome, suggesting a predictive role in surgically treated patients.[14,15] CCND1 amplification and overexpression has been identified as an important biomarker to evaluate outcome and treatment response.[16]

Though EGFR overexpression has been observed in approximately 90% of HNSCC tumors and is associated with poor prognosis and resistance to chemotherapy and radiation therapy, disappointingly, only about 10% of HNSCC cases respond to anti-EGFR agents.[17] This has been attributed to mechanisms of resistance to EGFR-targeted therapies. Afatinib, an oral small molecule ErbB family blocker, that irreversibly binds to ErbB1 (EGFR), ErbB2 (HER2), and ErbB4 (HER4), is being investigated in HNSCC treatment with encouraging phase II results and several ongoing phase III trials.[18] Besides EGFR inhibitors, inhibitors of FGFR and PIK3CA are all now available with appropriate genetic matching of tumor characteristics with correct inhibitor, a prospective promising area of future research. Thus, next horizon for targeted agents is to find correct combinations of targeted agents for individual tumors based on their genetic profiling.

Principles of tissue autofluorescence, tissue reflectance, or narrow band imaging (NBI) are being used as aids to facilitate early detection of HNSCCs. NBI (Olympus Medical Systems Corporation, Tokyo, Japan) is an endoscopic visualization technology which enhances mucosal surface texture and underlying vasculature by utilizing concept that wavelength of light determines the depth of penetration.[19] Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for detecting oral neoplasia with NBI ranged from 95% to 96%, 97–100%, 91–100%, 93–99%, and 97%, respectively. Optical coherence tomography (OCT) is analogous to ultrasound imaging except that it uses light rather than sound. High spatial resolution of OCT enables noninvasive *in vivo* "optical biopsy" and provides immediate and localized diagnostic information.[20] Confocal endomicroscopy is another noninvasive optical biopsy modality that helps in early diagnosis of oral premalignant lesions. Laser capture microdissection technology based on the extraction of cells from specimens in which exact morphology of both captured cells and surrounding tissue is preserved when combined with rapid immunohistochemical staining techniques help to detect biomarkers and protein fingerprint models facilitating early detection of OSCC.[21] Intensive evaluation of these technologies in prospective clinical trials is needed to find best ways to incorporate them into clinical practice to facilitate early detection of oral malignant lesions leading to improved outcome and survival.

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