Relationship Between Environmental Carcinogens and EGFR Targeting Anti-tumor Agents in Head and Neck Cancer

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Head and neck squamous cell carcinoma (HNSCC) ranks among the 10 most common cancers in the world and has been thought to correlate highly with environmental risk factors such as smoking, alcohol drinking, betel nut chewing and human papilloma virus infection.\textsuperscript{1} Among these risk factors, the betel nut chewing habit is the most regionally specific to South East Asian countries such as Thailand, Philippines, Papua New Guinea, and Taiwan. The mechanism that underlies the carcinogenesis in relation to betel nut chewing is complex, involving both physical and chemical etiologies. Repeated long-term exposure to betel nut-related carcinogens resulted in persistent damage of oral mucosa and is reflected in the high prevalence of buccal cancer in young male patients in Taiwan,\textsuperscript{2} which in turn generates social and economic burdens.

In recent years, the development of anti-epidermal growth factor receptor (EGFR) monoclonal antibody opened up a new era of therapy for head and neck cancer both in combination with radiotherapy and palliative chemotherapy.\textsuperscript{3,4} In the treatment of recurrent/metastatic head and neck cancer, a phase III randomized controlled trial showed a significant survival benefit in the group treated with platinum-based chemotherapy plus cetuximab combination versus the control group treated with platinum-based chemotherapy alone (10.1 months vs. 7.4 months for overall survival; 5.6 months vs. 3.3 months for progression-free survival), an unprecedented result over the past 30 years.\textsuperscript{4} However, it is interesting to note that response to anti-EGFR treatment still cannot be predicted. The potential mechanisms of resistance to EGFR-targeted therapy are being studied, including EGFR overexpression and amplification, as well as k-ras mutation.\textsuperscript{5-7}

The question of interest is whether or not anti-EGFR treatment exerts its effect on patients with long-term exposure to betel nut-related carcinogens, which may be involved in a complex of carcinogenic pathways. In a study published in the June 2010 issue of the Journal of the Chinese Medical Association, Chang et al\textsuperscript{8} retrospectively analyzed recurrent/metastatic HNSCC patients who received cetuximab-based therapy alone or in combination with other chemotherapy. In the study, 60% of patients had a betel nut chewing habit, 92% were male, and 20% of patients had buccal cancer. The results showed a high overall response rate and disease control rate in both the first-line chemotherapy group and the cisplatin-failure therapy group (54% vs. 20% in overall response rate; 62% vs. 50% in disease control rate) with acceptable toxicities [grade III/IV infection/fever (23% in the first-line group, 50% in the cisplatin-failure group) and neutropenia (23% in the first-line group, 25% in the cisplatin-failure group)]. This report reached an encouraging conclusion that cetuximab-based therapy is an effective and safe treatment choice for recurrent/metastatic HNSCC in an area in which betel nut chewing is popular. A more in-depth response analysis revealed a higher complete remission rate in the first-line therapy group with the addition of taxane as well as in the cisplatin treatment failure group with the addition of chemotherapy. Moreover, the survival analysis showed a better response to treatment in patients with 1st recurrent/metastatic disease and without betel nut chewing habit. The weakness of the study was that the sample population was small, rendering it difficult to draw a definite conclusion on the subject matter. However, the results did imply poor prognosis in the subgroup of patients who
fail to respond to cisplatin treatment and who have a habit of chewing betel nuts. The results also implied that aggressive combination treatment with anti-EGFR agents and chemotherapy may increase treatment response and result in better prognosis in suitable patients. However, selection bias was inevitable in such a retrospectively conducted study for patients accepting cetuximab-based therapies. Further prospective, large randomized trials using cetuximab combination therapy in this specific group of patients who have long-term exposure to betel nut-related carcinogens are warranted.

The gene mutations and associated changes in phenotype are usually complex in correlation with environmental carcinogens and cancer. In betel nut related carcinogens, EGFR overexpression and gene copy number amplification have been found to be associated with carcinogenesis. In the near future, patient selection for anti-EGFR based therapy, especially in areas with a high prevalence of betel nut chewing, holds promise for improving treatment outcomes in recurrent/metastatic head and neck cancer.

References


