Immunology of Head and Neck Cancer
Prospects for Immunotherapy

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Summary

Patients with squamous cell cancer of the head and neck region frequently have cell-mediated immune defects and anergy, which progress with disease. T lymphocytopenia and dysfunction, monocyte dysfunction, prostaglandins, antigen-antibody complexes, serum and cell suppressive factors, radiation therapy and poor nutrition with zinc deficiency all play a role. However, cell-mediated immunoreactivity to tumour is manifest in the majority of patients in blood and regional nodes, and in the tumour itself by tumour-infiltrating lymphocytes. Lymphocytes from these sources cloned in the presence of interleukin-2 ± tumour
extracts show relatively specific cytotoxicity against squamous cell cancer. Humoral immunity is intact, and increased IgA levels and antibodies reactive to tumour antigens are common. Tumour-associated antigens detected in tumour and serum include carcinoembryonic antigen, tumour polypeptide antigen, squamous cell cancer antigen, tumour antigen-4 and various mucin antigens. The mucin antigens, in particular, elicit T cell cytotoxicity.

Immunotherapeutic efforts in head and neck squamous cell cancer should logically employ T cell adjuvants, contrasuppression and immunorestoration. Nonspecific stimulation with bacille Calmette-Guérin (BCG), levamisole and other agents has not been successful. Encouraging results have been observed in limited trials with indomethacin, plasmapheresis and thymic peptides. Early trials with local administration of low dosages of interferon-α, natural interleukin-2 and a natural interleukin mixture have produced partial and complete regressions with no toxicity, with intense leucocyte infiltration indicating cell-mediated immunity. On the contrary, treatment with high dosages of recombinant interferon-α and interleukin-2 has yielded few responses with considerable toxicity. Combination strategies are warranted to improve upon this initial immunotherapeutic effort.

The vast majority of head and neck cancers are squamous cell carcinomas (SCC). These cancers occur most frequently in males approximately 60 years of age and over, and are generally related to smoking and often to alcohol (ethanol) consumption.[1] They are frequent, with approximately 42 000 cases/year in the US,[2] and are known to occur in association with immunological defects. Their immunology has been reviewed previously.[3-12]

At presentation, patients often display depressed cell-mediated immunity, as manifest by low or absent delayed-type hypersensitivity skin tests. B lymphocyte–related dysfunction is also apparent, with hyperglobulinaemia and circulating immune complexes. Monocyte/macrophage dysfunction with prostaglandin-mediated suppression accompanies these abnormalities.

These tumours are generally reacted to by the host with immune mechanisms. The ability of these immune mechanisms, particularly those related to T lymphocytes, to participate in resistance to this cancer is the subject of this review. Initial efforts with nonspecific immunotherapy have not been particularly rewarding. However, more recent efforts to restore delayed-type hypersensitivity and induce cell-mediated immunity to these tumours are encouraging. It is the purpose of this paper to: (a) review the immunology of head and neck SCC; (b) focus on the significant mechanisms of the immunodeficiency involved; and (c) propose methods to improve immunotherapy of the disease.

1. Natural History of the Disease

Head and neck SCC are generally staged according to the size of the initial lesion (T1-4), the degree of nodal involvement (N0-3) and whether metastases are present (M0-1), the so-called TNM classification. Stage at diagnosis is the most important predictor of outcome.[13] These tumours are treated by surgery, often radical, followed by irradiation if disease is locally advanced and likely to recur. Finally, multidrug chemotherapy is employed for advanced disease; however, its effect is generally only palliative.[14-16]

As a group, these tumours are curable by surgery and radiation in approximately 62% of patients, depending on the stage at diagnosis.[2] Recently, chemotherapy combined with radiotherapy has been shown to be equivalent to surgery and radiotherapy for laryngeal carcinoma, thus allowing vocal cord preservation for limited disease.[17] Survival curves reach a plateau in 2 to 3 years. Thus