Immunological Therapy of Breast Cancer
Current Status and Future Potential

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Summary

Clinical trials of immunotherapy in patients with breast cancer have been limited. Although immune function does not appear to be depressed in patients with operable breast cancer, immune function may play a role in preventing tumour recurrence in such patients. For example, 2 features associated with an adverse prognosis include peripheral blood lymphocytopenia and lack of reactivity against autologous tumour in skin windows.

A number of agents that specifically or nonspecifically augment immunity have been studied. These include levamisole, the interferons, interleukin-2, cyclosporin, tumour vaccines, monoclonal antibodies and immunotoxins. Most of these trials have involved treatment of patients with advanced disease, and little antineoplastic activity has been demonstrated in this setting. Randomised trials have found no proven benefit for treatment with interferon-α or levamisole in addition to standard chemotherapy in patients with breast cancer, although these agents may not have been used optimally in these studies.

Improved understanding of the biology of breast cancer is likely to result in
more rationally designed biological therapies employing entirely new treatment strategies, or using currently available drugs more effectively. Furthermore, levamisole combined with fluorouracil in patients with Duke's C colon cancer can result in an improved outcome when compared with fluorouracil alone. This suggests that carcinomas of glandular origin may be immunologically responsive, and that it may be possible to produce clinical benefit with immunological therapies even if the precise basis for the benefit has not been defined.

The prognosis for patients with advanced adenocarcinoma of the breast has not changed significantly over the past 40 years. Most of the clinical literature has focused on intensification of cytotoxic drug therapy, amelioration of its toxicity with haematopoietic growth factors, and the development of new cytotoxic and hormonal agents.

Recently, improved understanding of the biology of the disease has led to investigation of alternative biological strategies such as promoting tumour cell differentiation,[1] inhibiting the metastatic cascade,[2] impairing tumour angiogenesis,[3] blocking autocrine or paracrine growth factor loops,[4] and inhibiting expression of specific gene products that are responsible for the malignant cell phenotype.[4] Harnessing the immune system to kill cancer cells represents another potential strategy for breast cancer therapy. The ability of the immune system to generate an immunological response capable of rejecting an organ allograft suggests that these same mechanisms may be harnessed to mediate the rejection of malignant tumours.[5]

1. Immune Function in Breast Cancer

There have been scattered reports of clinically aggressive adenocarcinomas of the breast occurring in young women who have the acquired immunodeficiency syndrome (AIDS)[6] or who have had organ allografts.[7] However, the risk of breast cancer is not increased in immunosuppressed patients.[8] Nevertheless, quantitative and/or qualitative abnormalities of lymphocytes in the peripheral blood, primary tumour and regional lymph nodes have been described in patients with breast cancer.

These factors may influence the natural history of breast cancer. Peripheral blood lymphocytopenia has been associated with a poor prognosis.[9] Lymphocytic infiltration of the primary tumour has been associated with a poor prognosis in some reports, although it appears to be a favourable feature in medullary carcinoma of the breast.[10] Lymphocytes from regional axillary lymph nodes adjacent to a primary breast cancer have impaired cytotoxic activity against cultured human target cells.[11] This finding may be explained by the production of tumour-derived polypeptide growth factors, such as transforming growth factor-β, that are known to impair lymphocyte function.[12]

Axillary lymph node metastases and estrogen receptor-negative tumours are associated with a poor prognosis in breast cancer. These features are also associated with diminished peripheral blood natural killer (NK) cell activity.[13,14] NK cells are known to be important in immune surveillance. They are diminished in activity in patients with X-linked lymphoproliferative disorders and familial or sporadic melanoma.[15] This suggests that specific tumours may be associated with immunosuppression, or, conversely, that impaired immune surveillance may contribute to the development of certain cancers. Finally, reactivity in skin windows against autologous breast cancer cells predicts a decreased likelihood of recurrence, suggesting that more immunogenic tumours, or more immunocompetent patients, may have a better prognosis.[16]

2. Immunotherapy of Breast Cancer

Immunological approaches to cancer therapy may be either active or passive. Active immuno-