The article by Laheru and Jaffee offers an excellent summary of immunotherapies for gastrointestinal malignancies. Thoughtful descriptions of the antibody, cytokine, and cellular components of the immune system provide useful background information that facilitates an understanding of specific passive and active cancer immunotherapies. Immunotherapies that have demonstrated efficacy in colon cancer clinical trials, including levamisole (Ergamisol), passive monoclonal antibody vaccines, and bacillus Calmette- Guérin (BCG)–autologous tumor vaccines, are appropriately reviewed. In addition, novel approaches at varying stages of clinical testing are clearly summarized; these include the use of an anti-idiotypic antibody, genetically modified tumor and dendritic cells, recombinant protein, and viral and DNA vaccines. Some additional approaches, studies, and perspectives are also worthy of mention as a supplement to this review.

Interleukin-2 Gene Transfer in Colon Cancer
A phase I clinical trial of an interleukin-2 (IL-2) gene–modified autologous colon tumor vaccine has been completed and reported. In this study, colon cancer patients were found to have low frequencies of tumor cytotoxic T-cell precursors that were increased by this form of IL-2 gene therapy.[1] Similar findings with related gene-modified vaccines have been observed in other types of cancers.

Immunocytokines and Combination Immunotherapies
The results of clinical studies suggest that the concomitant systemic administration of immunopotentiating cytokines may significantly enhance the clinical efficacy of tumor antigen vaccines.[2] Unfortunately, however, the administration of systemic cytokines may also be associated with undesirable side effects that limit their clinical application. A potential alternative to cytokine administration is the employment of recombinant fusion proteins that combine the targeting characteristics of an antibody fragment with the immunopotentiating properties of the cytokines.[3] These chimeric molecules, termed immunocytokines, provide cytokine activity at selective sites that are dictated by the specificity of their antibody components while circumventing the toxicities associated with systemic cytokine administration.[3] Immunocytokines retain all of the activities of the antibody component, including target-cell binding, effector functions (complement-dependent cytotoxicity [CDC] and antibody-dependent cellular cytotoxicity [ADCC]), as well as normal cytokine function.[3] Studies in animal-tumor models have demonstrated that: (1) immunocytokines provide superior antitumor effects than their corresponding cytokines with less toxicity, and (2) the efficacy of genetically engineered tumor cell vaccines may be significantly enhanced by the concomitant administration of immunocytokines.[3]

An immunocytokine suitable for application in the treatment of gastrointestinal and other carcinomas is currently being evaluated in phase I clinical trials. The immunocytokine fusion protein, KS1/IL-2, is derived from a monoclonal antibody that is genetically fused with two IL-2 molecules. The monoclonal antibody component is reactive with the pancarcinoma antigen KSA. Interleukin-2 is an important cytokine in the generation of antitumor immune responses. It participates in the induction of both T-cell and natural killer[cc]cell immune responses that are...
complementary for tumor destruction. It is generally recognized that tumor cells that express major histocompatibility complex class I molecules may be eliminated by tumor antigen-specific CD8+ T cells, while tumor cells with decreased or absent class I expression are targets for elimination by natural killer cells. Hence, immunocytokines with IL-2 activity may enhance antitumor immunity through the induction of both T-cell and natural killer cell-mediated mechanisms. These findings indicate the potential value of combining complementary forms of immunotherapies to enhance antitumor effects.

**Radiation Sensitization by Immunotherapy**

Another interesting application of immunotherapy is to increase the efficacy of standard radiation treatment. In animal tumor models, interleukin-3 (IL-3) gene transfer sensitized tumors to the effects of radiation and stimulated antitumor immune responses that could eradicate metastatic disease. Interleukin-3 is known to stimulate antigen-presenting cells (macrophages and dendritic cells) that are required for the generation of systemic antitumor immunity. The IL-3-secreting tumors were more sensitive than wild-type tumors to radiation, and antigen-presenting and T-cell infiltrates increased following radiation therapy. The combination of IL-3 cytokine gene therapy with radiotherapy was synergistic, resulting in tumor cures that were not obtained with either therapy alone.

These findings support the value of future clinical evaluation of this multimodality, radiation-sensitizing, immunotherapeutic approach.

**Prophylactic Vaccines**

Although most preclinical and clinical studies of tumor vaccines have focused on their application as cancer treatments, we should not overlook the potential for these preparations to serve as true vaccines to prevent cancer. Useful parallels may be drawn from infectious diseases, where vaccines are generally employed for prophylactic, rather than therapeutic, purposes. Hence, it is possible that tumor vaccines may ultimately find greater success when applied as prophylactic, rather than therapeutic, agents.

Several barriers need to be overcome before prophylactic tumor vaccines are tested. First, the best tumor antigen targets and vaccination approaches remain to be identified. Current studies of various vaccination regimens in the therapeutic setting should provide important information that will enable us to select the optimal vaccines for future testing as prophylactic agents.

Second, the scope, logistics, and costs of trials to demonstrate the efficacy of prophylactic vaccines are significant. However, the precedent for and feasibility of such trials have been demonstrated in the recently completed studies demonstrating the efficacy of tamoxifen (Nolvadex) as a chemoprophylactic agent for breast cancer. Similar clinical trials for individuals at higher risk for the development of colon cancer can be considered once appropriate tumor vaccine candidates have been identified.

In this regard, the recent development of several transgenic animal tumors provides more realistic models to test the efficacy of both therapeutic and prophylactic vaccines. In contrast to previous transplantable tumors, these transgenic animals have been rendered tolerant to target tumor antigens and represent more realistic models for the evaluation of clinical cancer immunotherapies. Information from studies in these more sophisticated animal models, combined with the results of therapeutic vaccine clinical trials, will eventually lead to the identification of vaccines for which prophylactic testing can be justified.

**Summary**

In summary, the past clinical success of passive and active forms of immunotherapy and the present encouraging results with a variety of immunologic approaches in preclinical models and early clinical trials support the continued development of novel, multimodality, molecular immunotherapies for the future treatment and prevention of gastrointestinal malignancies.

**References:**


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