Immunobiology and Intraperitoneal Immunobiologics in Ovarian Cancer

Ralph S. Freedman, MD, PhD

Summary

Advances continue to be made in tumor immunology and in strategies to integrate the growing number of bioimmunotherapeutic molecules into the treatment of ovarian cancer, as well as other malignancies. Extensive studies have provided support for antigen-driven T-cell activation in vivo. The number of known tumor antigen epitopes is expanding, although advances in this area remain behind that of melanoma. Evidence suggests that the tumor environment is contributing to a state of in vivo immunosuppression; however, in vitro experiments and laboratory correlative studies also show that immune suppressor activity might be reversible. These findings could lead to new approaches, such as the use of antibodies or cytokines to overcome the immunosuppressive effects, in addition to the more established surgical and chemotherapeutic debulking.

Both prophylactic and therapeutic bioimmunotherapeutic strategies require pharmacodynamic and immunologic end points that can guide each phase in the development of an effective approach. Review of systemic and intraperitoneal (IP) immunotherapy trials of interferon (IFN) \(\alpha\), IFN\(\gamma\), and interleukin 2 (IL2), as well as newer agents such as IL12 and Flt3 ligand, overall continues to offer promise of a role for bioimmunotherapy in the treatment of ovarian cancer. Future developments lie in the improved target specificity of activated cells and cell-surface–binding molecules and in a systematic plan for combining chemotherapy with cytokines, growth factors, and polyvalent vaccines that are based on the \textit{in vivo} dynamics of each agent. Another totally different approach, which could set a new paradigm, might be to target cells from the inflammatory immune system, which could contribute to tumor growth, invasion, and metastasis.

Key Words: Bioimmunotherapy; intraperitoneal therapy.

Developments in bioimmunotherapy have been spurred by advanced knowledge of tumor immunology and the availability of an increasing array of recombinant and other molecules that target specific sites in the immune system.

Cellular immunity incorporates adaptive and innate components. We extensively reviewed the subject in a previous study (1). The dendritic cell (DC) is a key cellular element for processing tumor cell antigens, and it eventually matures to perform three main functions. These functions relate to the activation of cells belonging to the adaptive (CD3+CD4+ T-cell receptor (TCR) αβ and CD3+CD8+TCRαβ+) or innate systems (natural killer [NK], CD3+ TCRγδ, or monocyte [MO]/macrophages [MAs]). The functions include presentation of tumor-derived peptide in the context of the major histocompatibility complex (MHC) to CD4+ and CD8+ T cells complemented by co-stimulation through B7 and other surface molecules, and the production of IL12, which is able to stimulate both adaptive and innate immune systems. Production of IFNγ by certain T cells, NK cells, and T γδ cells is a vital component of both adaptive and innate immunity and participates in both MHC-restrictive killing by CD8+ T cells and the non–MHC-restricted killing exhibited by NK, T-γδ cells, and MAs. Progress has been made in understanding the receptor–ligand interactions of the innate immune cells. Interferon γ may produce antitumor effects through several different mechanisms, including direct inhibition of growth, up-regulation of MHC molecules to make tumor cells better targets for the adaptive system, and induction of superoxides or nitric oxide by MAs activated by IFNγ and tumor necrosis factor (TNF). Interferon-γ also increases activity of the indolamine deoxygenase enzyme that converts tryptophan to kynurenine, which is then converted to hydroxykynurine, which is highly toxic not only to human tumor cells (2) but also to activated T cells. IFNγ has antiangiogenic effects, which are probably mediated through the chemokine IP10, but possibly also through down-regulation of the integrin receptor pathways on tumor endothelial cells.

Evidence for specific T-cell activation in vivo in ovarian cancer follows criteria that have been set for melanoma, and includes the development of specifically activated T-cell lines or clones from tumor-infiltrating lymphocytes (TILs); demonstration of antigen-dependent and -independent cytokine production upon co-incubation of these T-cell lines or clones with autologous tumor; the demonstration of MHC-restricted tumor cell activity; and, importantly, the clonal expansion of TCRαβ clones, in vivo, as we have recently demonstrated (3). However, even the discovery of clonally expanded T cells with tumors in vivo does not determine their type of activity in vivo.

The number of tumor antigen epitopes in ovarian cancer remains small, relative to that shown in malignant melanoma. Most of the work in ovarian cancer relates to studies conducted with HER2/neu peptides that express HLA A2 motifs, demonstrated by Ioannides (4,5), Peoples (6,7), and extensive studies conducted by Disis (8). More recently, the human telomerase reverse transcriptase protein component of the telomerase enzyme and the alpha folate receptor