Cytokine Gene Therapy for Malignant Pleural Mesothelioma

Anil Vachani, MD, Daniel H. Sterman, MD, and Steven M. Albelda, MD

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The treatment of advanced pleural malignancies, such as malignant pleural mesothelioma (MPM), remains generally ineffective despite the use of surgery, external beam radiation therapy, and chemotherapy individually or in combination.[1,2] Given the current lack of effective therapies, new treatment approaches for MPM are clearly needed, including the novel approach of intrapleural genetic immunotherapy. MPM is a particularly attractive target for gene transfer studies because of the paucity of effective therapies and the relative accessibility of the tumors in the pleural space for delivery of experimental therapies. Because MPM rarely metastasizes early to distant sites, treatment of the primary tumor can lead to significant palliative benefits and may potentially prolong survival.

Cancer gene therapy is defined as the transfer of genetic material, including full-length genes, complementary DNA, RNA, or oligonucleotides, into cancer or host cells for the ultimate purpose of killing an autologous tumor. The basis for cytokine gene therapy in MPM lies not only in the direct antiproliferative effects on mesothelioma cells but also in the ability of certain cytokines to activate systemic, intrapleural, and intratumoral immune effector cells. Although mesothelioma is well known to inhibit host cellular and humoral anti-tumor immune responses, animal and clinical data support the use of immunotherapeutic approaches.[3,4] Prolonged local cytokine expression can activate tumor-associated dendritic cells to phagacytose tumor antigens (after the induction of tumor cell apoptosis) and to express these antigens on major histocompatibility complex heterodimers in conjunction with costimulatory molecules. These activated dendritic cells can then migrate to regional lymph nodes, where they stimulate the proliferation of CD4 and CD8 lymphocytes, inducing anti-tumoral cytotoxicity at distant tumor sites. Several published phase I and phase II clinical trials have documented mesothelioma tumor responses to intrapleural infusion of interleukin-2 (IL-2), interferon (IFN)-α, and IFN-γ.[5–10]

INTERFERONS

IFNs (especially type I IFNs like IFN-α and -β) are known to inhibit tumor cell growth and stimulate the immune system.[11] IFNs have immunoregulatory effects on antibody production, natural killer (NK) and T-cell activation, macrophage function, delayed-type hypersensitivity, and major histocompatibility complex antigen expression, as well as antiproliferative effects and anti-angiogenic properties.[12–16] The results of human clinical trials of IFNs in the treatment of various solid tumors have yielded disappointing results. This is, in part, related to the short plasma half-life of IFNs after systemic, local, or subcutaneous injection with a resulting lack of sustained tissue levels.[17] Doses of systemic IFNs necessary to achieve intratumoral levels equivalent to those found in vitro to induce cytostatic and anti-proliferative effects are associated with significant, and likely intolerable, toxicity.[18] The rationale behind the use of gene transfer approaches to cytokine therapy is that local, continuous delivery and production of IFNs in and around tumors would compensate for the short half-life of IFNs, inhibit tumor growth and metastasis, and minimize systemic side effects.

IFN-β gene transfer in animal models of various malignancies (both xenografts and autologous tumors) has demonstrated impressive anti-tumor effects (Figure 1).[19–22] Preclinical studies in MPM have demonstrated that: 1) an adenoviral vector encoding mouse IFN-β (Ad.IFN-β) had dramatic therapeutic efficacy in syngeneic animal models of MPM;[23–25] 2) intraperitoneal and intratumoral injections of Ad.IFN-β showed significant activity both in the injected tumor and in distant tumors;[23–25] and 3) in these models, this effect was immunologic, in large part because of the generation of cytotoxic T-lymphocytes directed against as yet undetermined tumor antigens and activation of natural killer cells. These experiments served as the basis for the initiation of a phase I clinical trial.

We hypothesized that the intracavitary administration of Ad.IFN-β through an indwelling pleural catheter would be an effective local and systemic treatment for advanced thoracic malignancies, such as MPM. After confirming vector safety in extensive rodent experiments, we initiated a single-center dose-escalation phase I clinical trial assessing the safety of single-dose intrapleural infusion of Ad.IFN-β in patients with MPM (and patients with metastatic pleural

Thoracic Oncology Research Laboratory, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania.

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Address for correspondence: Anil Vachani, MD, Pulmonary, Allergy, and Critical Care Division, 1016A Abramson Research Center, 3615 Civic Center Boulevard, Philadelphia, PA 19104. E-mail: avachani@mail.med.upenn.edu

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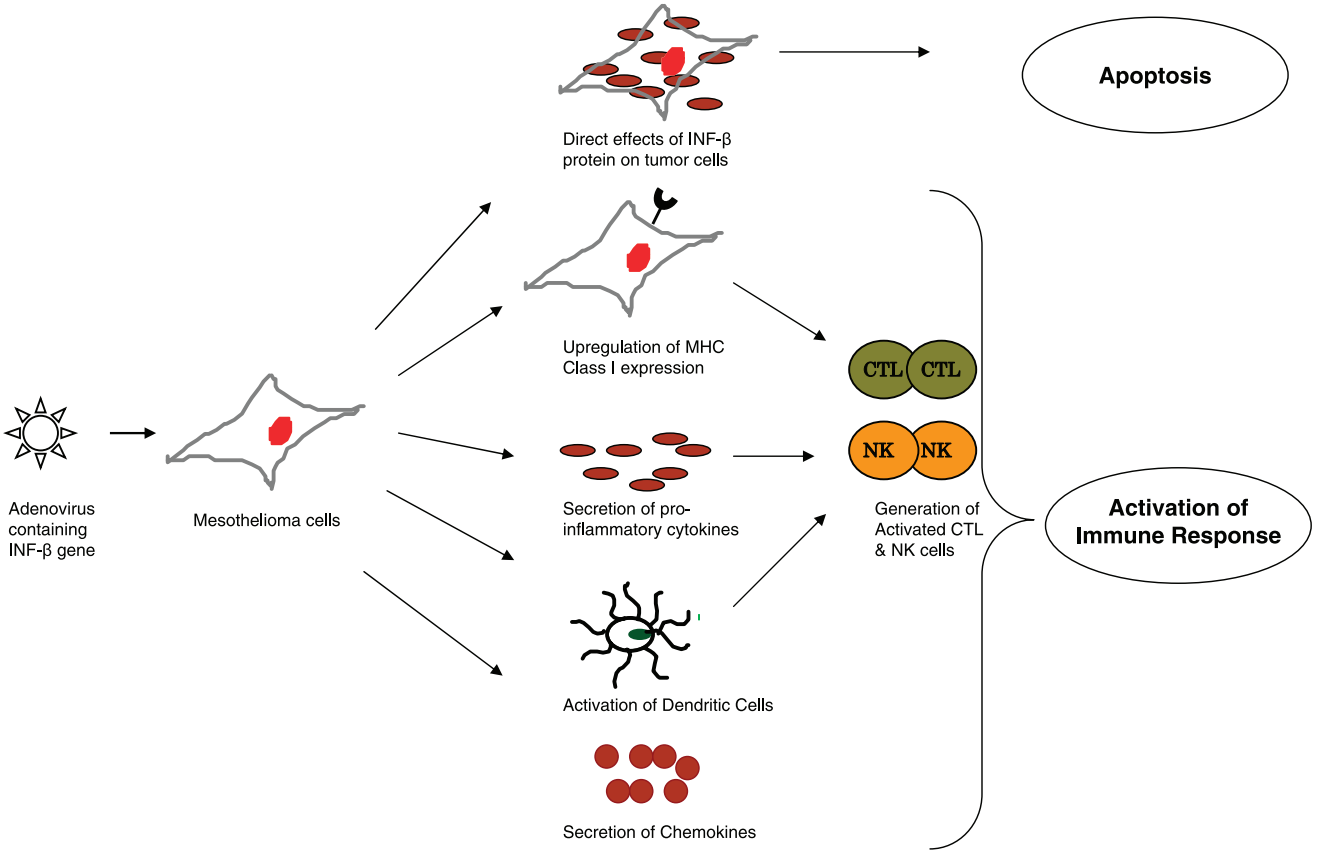

FIGURE 1. Antitumor mechanisms of interferon (IFN)-β gene therapy for malignant pleural mesothelioma. IFN-β has direct effects on the tumor and multiple effects leading to activation of the immune response. MHC, major histocompatibility complex; CTL, cytotoxic T-lymphocyte; NK, natural killer.

effusions).[26] Secondary goals of the phase I clinical trial included evaluation of induced anti-vector and anti-tumor immune responses, viral shedding, and any discernible clinical responses. Given the ability to sample the pleural space with the indwelling catheter, we could also monitor intrapleural gene expression and immunologic responses. The results of this trial demonstrated that intrapleural Ad.INF-β was well tolerated, generated anti-tumor immune response in almost all of the patients, and resulted in encouraging anti-tumor activity (unpublished data).[26]

FUTURE DIRECTIONS

Although we may be able to generate anti-tumor responses with intrapleural Ad.IFN-β, we believe that, in bulky tumors, this will not likely be sufficient to effect a significant clinical response because of a low effector cell to target cell (tumor) ratio, strong immunosuppressive effects (mediated by factors such as prostaglandin E2, transforming growth factor β, or interleukin-10) within the tumor microenvironment, and restrictions of leukocyte trafficking. It is our hypothesis that the generation of anti-tumor reactive T-cells by administration of Ad.IFN-β will not be optimally effective unless other approaches are used to block immunologic checkpoints and enhance trafficking into tumors. Studies performed by our group have shown the utility of multiple vector dose administration, tumor debulking,[27] adjuvant COX-2 inhibitors,[28] and immunomodulatory chemotherapy (with drugs such as gemcitabine) when combined with Ad.IFN-β gene transfer. A second phase I study of repeated-dose intrapleural Ad.INF-β is currently ongoing at our institution, and the combination of Ad.IFN-β with surgery, chemotherapy, and/or COX-2 inhibitors will be incorporated into future phase II trials.

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