Gene Therapy for Ovarian Cancer

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Advances in molecular virology and biotechnology have led to the engineering of vectors that can efficiently transfer genes to target cells. Gene therapy strategies were developed along two lines: Cytotoxic approaches

The recent advances in cell and molecular biology of cancer have elucidated some of the mechanisms underlying malignant transformation, tumor cell migration, metastasis, angiogenesis, and cell response to chemotherapy. Advances in molecular virology and biotechnology have allowed for the engineering of vectors that can efficiently transfer genes to target cells. As a result, gene therapy strategies for the treatment of cancer were developed along two fundamental directions. Cytotoxic or suicide gene therapy approaches entail the transfer of genes that encode enzymes able to convert inactive prodrugs into cytotoxic drugs. Only transfected cancer cells expressing the specific enzyme become susceptible to killing. Corrective gene therapy strategies aim at repairing specific molecular alterations occurring in signal transduction mechanisms that control the cell cycle or induce apoptosis.

Gene Therapy Vectors

The Recombinant DNA Advisory Committee has approved hundreds of gene therapy protocols for the treatment of genetic diseases or cancer. Although gene therapy strategies have produced highly promising results in preclinical in vitro and animal models, their application in clinical practice has proven to be much more difficult. A fundamental problem concerns the efficiency of gene transfer. Viral vectors remain the vectors of choice, mainly because of their high efficiency of transfection. After all, viruses have evolved successful strategies for introducing their genome into eukaryotic cells and using the host cell biochemical machinery.

The vast majority of phase I trials employ viral vectors, but some use DNA protein complexes, DNA particles, ribozymes, or lipid-based vehicles. To minimize side effects, viral vectors are rendered replication-incompetent. To date, several vectors have been developed that are associated with significant limitations related to low efficacy, inability to penetrate deeply in tumor nodules, inactivation by the immune system, and undesired side effects (Table 1). To enhance efficacy, inserted genes (transgenes) are positioned under the control of a strong exogenous promoter. A reporter gene, such as the Escherichia coli LacZ gene encoding beta-galactosidase, is also inserted to assess the efficacy of gene transduction.

Adenovirus

Adenoviral vectors are currently the vectors of choice in gene therapy, including cancer gene therapy. [1] Adenoviral vectors are remarkably efficient, but yield only transient expression of therapeutic genes and are generally administered repeatedly to lengthen the duration of gene expression. Adenoviruses infect dividing and nondividing cells, and can be produced relatively easily on a large scale. They are stable, may be manufactured without contamination by replication-competent adenovirus (RCA),[2] and can accommodate up to 7.5-kb transcripts. Backbones have been derived from Ad2 and Ad5 serotypes, both of which belong to the wild-type-C adenovirus subgroup.

The vitronectin receptor alpha(v) beta(3) integrin and the coxsackie/adenovirus receptor mediate virus entry into human cells through clathrin-coated vesicles.[3] The viral genome remains extrachromosomal in the nucleus. Recombinant adenovirus is produced on appropriate packaging cell lines complementing the missing genes. The early genes specifically, E1 were first targeted because they control viral replication and regulate the expression of late genes. Substitution of E1A and E1B genes by a designated transgene led to the creation of the first generation of adenoviral vectors.

Due to the high likelihood of recombination events occurring during manufacturing in vitro, engineering of strains lacking only one gene were characterized by a prohibitive degree of
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Replication-competent adenovirus (RCA) contamination. This translated to high toxicity, particularly hepatotoxicity, considering the elevated liver tropism of the wild-type virus. A second-generation virus was then produced by adding an additional mutation in the E2A or E3 regions.[4] This improved the toxicity profile of the vectors by dramatically decreasing RCA contamination.

Administration of adenovirus is followed by an intense inflammatory and immune response. An early innate response consists of the release of inflammatory cytokines such as interferon (IFN)-gamma, interleukin (IL)-1, and IL-6 as well as the recruitment of an acute inflammatory infiltrate followed by a specific neutralizing antibody and T-cell response.[5] Both the transgene and viral genes expressed by transfected cells are cross-presented on major histocompatibility complex (MHC) class I or II sites, triggering specific CD8- and CD4-positive T cells. An intense inflammatory reaction in proximity to the tumor may enhance tumor immune recognition. However, immune-mediated vector neutralization may pose marked limitations on the transduction efficacy of the vector.

We and others have recently demonstrated the presence of neutralizing antibodies in the serum and peritoneal fluid of patients with epithelial ovarian cancer that significantly decrease the efficacy of adenoviral vectors in vitro. However, the presence of antiadenoviral antibody titers did not appear to compromise the efficiency of gene transfer in a phase I trial of adenoviral-based gene therapy for pleural mesothelioma conducted at our institution.[6] Nevertheless, there is still considerable concern about the limitations posed by the immune system, particularly if repeated administrations of vectors are planned. A third-generation adenoviral vector with somewhat decreased immunogenicity was recently produced by the deletion of the E4 region (in addition to E1 region) and preservation of the E3 region. The protein product of E3 inhibits MHC I transport to the cell surface, thereby preventing immune recognition of adenovirus-infected cells.

To address the concerns of RCA contamination and immune-mediated response, "gutless" or "gutless" adenovirus vectors that contain no viral genes have been generated.[7] These vectors accept up to 38 kb of foreign DNA. Gutless adenovirus vectors are replication-deficient and require helper viruses for propagation. One advantage of gutless vectors is that they are less immunogenic and, by using helper viruses derived from different adenovirus serotypes, production of host antibodies can be directed away from the therapeutic gutless vector. Gutless adenovirus vectors are showing promise in gene therapy. In mice, sustained expression of transgene was seen after a single injection, with no serious virus-associated toxicity.[8]

Epithelial ovarian cancer cells are susceptible to infection by adenoviral vectors.[9] We recently demonstrated that an E1/E4-deleted adenovirus was similarly efficacious to an E1/E3-deleted one in several epithelial ovarian cancer cell lines (unpublished observation). Current investigation is focusing on improving the tissue selectivity of adenoviral vectors. Crosslinking of adenoviral particles to basic fibroblast growth factor has proven to significantly increase the binding of adenovirus on epithelial ovarian cancer cells (SKOV3.ip), resulting in a 10-fold enhancement of its efficacy in vitro.[10] Furthermore, the incorporation of an Arg-Gly-Asp (RGD)-containing peptide to the HI loop of the adenovirus fiber knob through genetic engineering directs the virus away from coxsackie/adenovirus receptor binding sites and enhances its binding to the ovarian cancer cell surface.[11]

**Adeno-Associated Virus**

Adeno-associated virus has a 4.7-kb single-stranded DNA genome surrounded by a protein coat. Adeno-associated virus is not autonomous; in the absence of a helper virus, adeno-associated virus enters a latent state of infection, while coinfection by an adenovirus or herpesvirus enables adeno-associated virus to replicate.[12] Its genome has at least six transcripts with three internal promoters and two inverted terminal repeats. Construction of recombinant adeno-associated virus vectors can be accomplished by stripping off the gene sequences encoding viral structural proteins and generating a backbone with the two inverted-terminal repeats surrounding the inserted transgene. A packaging cell line is necessary for viral replication and production.

Wild-type virus integrates at a specific site on human chromosome 19. Adeno-associated virus vectors also integrate into host DNA for sustained gene expression. Adeno-associated virus proteins are not toxic to cells. Although 80% of the population is seropositive, adeno-associated virus is not associated with any known disease in humans, and an existing immune response does not impair the efficiency of transfection. Moreover, adeno-associated virus infection is not accompanied by inflammation or generation of a strong recall immune response.[13]

Adeno-associated virus shows promise in the setting of gene therapy because it infects a wide variety of cells. Its ability to infect both dividing and nondividing cells may be a major advantage in targeting tumors with low S phase. Sustained expression from adeno-associated virus vectors has been observed in several tissue types. Epithelial ovarian cancer cells harvested directly from
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Herpes Simplex Virus

Herpes simplex virus (HSV) is an enveloped double-stranded DNA virus of approximately 150 kb capable of infecting a great variety of human tissues. The HSV enters the cells through at least three identified receptors. Manipulation of the HSV genome has generated a great variety of vectors, including replication-incompetent virus vectors and amplicons.[14] Amplicon vectors are derived from plasmids that carry HSV genes, including the HSV origin of DNA replication and the packaging signals, together with bacterial genes. Amplicon vectors require the presence of a helper virus to carry out transgene expression. Recombinant vectors contain full-length HSV genomes, in which various viral genes have been deleted and substituted by transgenes. Different strategies have been followed for the generation of replication-incompetent HSV vectors, but they invariably affect key genes controlling viral replication, such as the ribonucleotide reductase, thymidine kinase (tk), the UL5, or the ICP34.5.[15] In addition, because the HSV genome contains at least 30 nonessential genes (ie, not essential for viral propagation in culture), multiple genes may be deleted without compromising vector production. Herpes simplex virus vectors, therefore, offer unique opportunities for multiple transgene insertion. Ovarian cancer cells are particularly susceptible to infection by HSV vectors.[16,17] The advantages of HSV vectors include the feasibility of large-scale production, versatility of the vector system, the ability to carry large or multiple transgenes, and the ability to induce direct toxicity even in the absence of replication. The application of HSV vectors may be hindered by preexisting immunity against HSV-1, which may be highly prevalent in the adult population. It is possible that HSV-neutralizing antibodies present in the serum or peritoneal fluid may decrease the efficacy of HSV-mediated gene therapy.

Retroviruses

Retroviruses are diploid positive-strand RNA viruses that replicate in the host through an intermediate step of DNA reverse transcription. The DNA transcribed on the viral RNA template is subsequently integrated into the host genome in a pseudorandom fashion, and the host nuclear machinery is used to produce RNA copies of the virus.[18] The murine leukemia virus was first used to construct vectors, but lentiviruses such as recombinant human immunodeficiency virus (HIV) strains are also currently being tested. Because of viral genomic integration, this strategy offers the advantage of long-term gene expression. Almost 20 years of experience with retroviral vectors has confirmed their feasibility and safety of administration. The major concern about retroviral vectors relates to insertional mutagenesis.[19] The pseudorandom insertion of genes into the host genome might disrupt a tumor-suppressor gene or modify (amplify) a growth-promoting gene, resulting in tumorigenesis (as exemplified by the action of the murine leukemia virus in mice). A second potential concern is related to incidental insertion of transgenes into the germ line. Although this phenomenon has been described in mice, no further experiments in animals have substantiated this concern. A potentially attractive characteristic of retroviruses is related to the lack of immune response following their administration, as retroviruses result in the production of a single transgene but no significant viral proteins. In addition, since some of these viruses are of murine extraction, no preexisting immunity has been encountered in humans. This would facilitate repeated administration of the virus without loss of its potency.

Liposomes

Direct gene delivery of plasmid DNA by relatively inert vehicles may represent a feasible alternative to the use of viral vectors. Liposomes are amphipathic lipids containing a hydrophobic domain and a hydrophilic domain composed of hydrocarbon chains such as fatty acids. Anionic liposomes do not bind DNA directly and offer limited packaging ability for gene therapy. Cationic lipids are mixed with a fusogenic lipid (such as dioleoylphosphatidylethanolamine, or DOPE) to form liposomes that are positively charged and bind DNA with great affinity.[20] Nonspecific ionic interactions often facilitate liposome binding to the cell surface; the complexes cross the cell membrane possibly through a fluid-phase endocytosis mechanism, but fusion mechanisms may also be important for some compounds. Liposomes are not associated with the toxicity of viral vectors and do not generate as potent an immune response. They are easy to produce on a large scale and offer the advantage of carrying
transgenes up to 50 kb in size. However, their transduction efficiency is significantly lower than viral vectors, and expression of liposome-delivered transgenes is transient. Cationic liposomes have proven efficient in delivering transgenes to a large variety of malignant cells in vitro. In vivo, liposomes have been used intraperitoneally and intravenously and have proven to be safe. Intratumoral injections have also been described. The uptake of liposomes by epithelial ovarian cancer cells is efficient,[21] thus supporting their use in intraperitoneal or systemic gene therapy for that disease. One potential problem with cationic liposomes is that they are avidly taken up by the reticuloendothelial cell system.[22] Stealth technologies may need to be implemented to increase the tumor selectivity of these agents. Moreover, significant work still needs to be done in order to improve the transfer efficiency and tumor selectivity of liposomes.

**Cancer Gene Therapy Strategies**

**Cytotoxic Gene Therapy**

Cytotoxic, or suicide, gene therapy entails the introduction into tumor cells of a specific gene that encodes an enzyme capable of converting a prodrug into a highly toxic drug. This conversion only takes place within the cells that express the transgene. The most frequently used mechanism involves the tk of HSV, which allows for the phosphorylation of ganciclovir into ganciclovir monophosphate in cells expressing the transgene.[23] This product is further phosphorylated twice into ganciclovir triphosphate by mammalian kinases, to become a potent inhibitor of DNA and RNA synthesis. Multiple other systems of enzymes and prodrugs with different advantages and limitations have been tested.

Incorporating ganciclovir triphosphate into DNA inhibits DNA polymerase and ultimately leads to DNA fragmentation followed by apoptosis. Ganciclovir induces cell death in a cell-cycle-dependent manner because incorporation of the triphosphate metabolite into DNA requires the cell to enter S phase. This provides a mechanism for tumor selectivity. Great enthusiasm was generated by studies indicating the existence of "bystander" amplification mechanisms that cause cell death in nontransfected nearby cells.[24] Initial studies, in fact, indicated that it was enough to transfect 5% to 15% of the cells in vitro in order to achieve 100% killing with the HSV-tk/ganciclovir system.

Diffusion of ganciclovir triphosphate toxic metabolite occurs through gap junctions into neighboring cells. Moreover, the Fas/Fas ligand (FasL) system may be involved in apoptosis induced by HSV-tk, because Fas, FasL, and two downstream caspases were found to be increased in tk/ganciclovir-treated tumor cells undergoing cell cycle arrest and apoptosis.[26] HSV-tk cytotoxic therapy may result in the generation of an antitumor immune response (Table 2), which could amplify the effect of cytotoxic gene therapy. In fact, tk/ganciclovir cytotoxic therapy has proven more efficacious in immunocompetent than in immunodeficient mice.[27]

The immunogenicity of tumors treated with HSV-tk and ganciclovir appears to be related to the modality of cell death and up-regulation of heat-shock proteins. A specific CD4- and CD8-positive T-cell infiltrate was seen in tumors undergoing necrosis following tk/ganciclovir treatment.[28] The cytokine response suggested a T-helper cell type 1 (TH1) lymphocyte response, including increased expression of IL-2, IL-12, IFN-gamma, tumor necrosis factor-alpha (TNF-alpha), and granulocyte-macrophage colony-stimulating factor (GM-CSF). Furthermore, stimulatory molecules such as B7 and ICAM were up-regulated together with MHC class I molecules in treated cells. Other suicide gene therapy systems have been tested experimentally (Table 3). Many of them use similar bystander effects and generate antitumor immune responses.

**Ovarian Cancer Studies**

Ovarian cancer cells are sensitive to the tk/ganciclovir cytotoxic system delivered through adenoviral or retroviral vectors as well as liposomes.[29] Multiple studies in vitro and in vivo in the immunodeficient mouse model have documented the ability of the tk/ganciclovir system to induce cytotoxicity, reduce tumor burden, and increase survival. We demonstrated that epithelial ovarian cancer cell lines SKOV3, CaOV3, OVCAR3, and A2780 are susceptible to killing by tk/ganciclovir in a dose-dependent manner. A single intraperitoneal dose of 1 million × 10⁵ particles of an E1/E3-deleted adenoviral vector carrying tk under a Rous sarcoma virus (RSV) promoter resulted in a significant reduction of tumor burden. This effect was even more pronounced after repeated intraperitoneal administrations (personal observations).

The use of HSV-tk/ganciclovir to enhance the antitumor immune response in ovarian cancer has been explored by Scott Freeman.[30] This author engineered the PA-1 human ovarian teratocarcinoma cell line to express HSV-tk through retroviral transfection. Intraperitoneal inoculation of these cells in mice followed by ganciclovir treatment led to regression of established
intraperitoneal adenocarcinoma. Tumor response was probably mediated by bystander and/or immune mechanisms, as established tumors are not directly transduced with HSV-tk. It is possible that inflammation in proximity to tumor may have contributed to unmasking of tumor antigens and the generation of the immune response. In fact, histologic analysis of tumors revealed that PA-1 cells were adherent on tumor nodules, and an intense inflammatory reaction had developed within tumors where PA-1 cells had adhered.

Based on promising preclinical studies, clinical trials using HSV-tk/ganciclovir cytotoxic gene therapy have been initiated in patients with advanced or recurrent epithelial ovarian cancer.[31] Dose-escalation studies using intraperitoneal administration of an adenoviral vector carrying HSV-tk have indicated that this strategy is safe, but no significant tumor responses have been seen thus far. Further studies with larger volumes of patients are required to assess the therapeutic efficacy of this strategy.

**Corrective Gene Therapy**

Corrective gene therapy strategies are being tested clinically in ovarian cancer (Table 4). These therapies may be divided in two main groups: replacement therapies and neutralization therapies. In tumors with documented loss of a gene function, wild-type genes are delivered to achieve normal levels of expression or overexpression of the wild-type gene within tumor cells, resulting in apoptosis or cell-cycle arrest. Examples of this process include the administration of p16, p21, p53, and BRCA1 genes.[32] In tumors with documented overexpression of oncogenes, ablative gene therapies may be carried out to neutralize oncogene function.

**BRCA1/2**

The molecular aspects of hereditary ovarian cancer have been partially elucidated with the identification and cloning of BRCA1 and BRCA2 genes, which appear to be mutated in some patients with hereditary ovarian/breast cancer. BRCA1 appears to be involved in tumor-suppressor pathways. The observation that BRCA1 overexpression blocks cell-cycle progression via p21 and causes tumor-growth inhibition mediated by the retinoblastoma gene (even in cells without BRCA1 mutation) led to preclinical gene therapy studies with a splice variant of wild-type BRCA1 gene (BRCA1sv) delivered via a retroviral vector.[33] In vitro and animal studies indicated that overexpression of BRCA1 induced arrest of tumor growth in epithelial ovarian cancer. A phase I clinical trial was conducted at Vanderbilt University Cancer Center in patients with sporadic ovarian cancer, none of whom harbored germ-line BRCA1 mutations.[34] Patients received one to three intraperitoneal injections of retroviral vector carrying the BRCA1sv gene at a dose of 10^13 to 10^10 vector particles. Toxicity included self-limiting clinical peritonitis, which was observed in 25% of patients. An antiretroviral antibody response was seen with higher doses, and gene transfer was documented by Southern blot in approximately 5% to 10% of tumor cells in laparoscopic biopsy material. Of 12 initially reported patients, 4 progressed, 7 displayed stable disease, and 1 achieved a partial response. Notably, the authors saw no correlation between antibody response and vector inactivation. However, they did observe a trend for higher gene expression in patients with low total complement activity (CH50), although there was no statistical correlation.

**p53**

Gene therapy with tumor-suppressor genes and genes involved in cell-cycle control have also been tested in epithelial ovarian cancer and other solid malignancies. Approximately 50% to 75% of epithelial ovarian cancer specimens harbor alterations in the p53 tumor-suppressor gene. Loss of p53 may be a late event in ovarian carcinogenesis but may contribute to chemotherapy resistance and represents an independent prognostic factor for a poor outcome.[32] In vitro and in vivo experiments showed that Bax (a transcriptional target of p53) and p16 (a cyclin D inhibitor involved in regulation of the cell cycle) might be appropriate targets for corrective gene therapy. However, most experience has been with the p53 tumor-suppressor gene.

Preclinical evidence suggests that p53 corrective gene therapy via adenoviral or retroviral vectors or liposome-plasmid DNA complexes results in an increased amount of apoptosis or cell-cycle arrest in epithelial ovarian cancer cells in vitro, while tumor regression was seen in vivo in mouse models.[29] Epithelial ovarian cancer cells transfected with wild-type p53 gene become more sensitive to DNA-damaging agents such as platinum.[35] Adenoviral p53 gene therapy was recently initiated in patients with epithelial ovarian cancer. Intrapерitoneal inoculation with p53 was reported in 37 women at a single dose of 7.5 × 1010 to 7.5 × 1013 particle-forming units. No significant complications occurred, and a reduction in CA-125 levels was seen in more than half of the patients.[36]

**HER2/neu**

HER2/neu (c-erbB2) is an oncogene encoding a 185-kd epidermal growth factor receptor-related protein with tyrosine kinase activity overexpressed in 30% of epithelial ovarian cancers and other solid tumors.[32] HER2/neu overexpression is correlated with malignant transformation and metastasis. Deshane et al engineered a gene encoding a monoclonal
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initial speculation that p53 inhibits adenoviral replication prompted the engineering of a recombinant Adenoviral E1B gene encodes a 55-kd protein that inactivates the p53 tumor-suppressor gene. Another oncolytic agent of potential interest is the E1B-defective adenovirus ONYX-015.

ONYX-15 Oncolytic HSV-1 appears promising and warrants testing in epithelial ovarian cancer. Lysis in epithelial ovarian cancer cells in vitro but spared normal human mesothelial cells. HSV-G207 induced a dose-dependent on the p53 status of the cells, which may partially account for the fact that chemotherapy resistance does not affect the sensitivity of epithelial ovarian cancer cells to HSV oncolysis. We further investigated the tumor specificity of HSV-G207, a doubly deleted HSV-1 lacking ICP34.5 and ribonucleotide reductase that regulates viral proliferation. HSV-G207 induced a dose-dependent lysis in epithelial ovarian cancer cells in vitro but spared normal human mesothelial cells. ONYX-15 Oncolytic HSV-1 appears promising and warrants testing in epithelial ovarian cancer.

**Oncolytic Agents**

The direct treatment of tumors with replication-competent viruses is not a novel idea. A number of studies undertaken in the 1950s and 1960s with direct intratumoral injections of wild-type viruses had limited success. The viral approaches were abandoned, however, because of the inability to attenuate viruses. With the advent of molecular biology and recombinant technologies, mutant viruses have been generated, renewing interest in virus-based tumor therapies.

**HSV-1 Mutants**

Replication-restricted HSV-1 mutants have been generated in several laboratories by altering genes that control viral replication, such as thymidine kinase (UL23) or the ICP6 gene (UL39) encoding the large subunit of HSV ribonucleotide reductase. HSV oncolytic agents have also been generated by altering both copies of the RL1 gene. Its product, the ICP34.5 protein, is critical for neurovirulence and plays an important role in viral replication, viral exit from infected cells, and prevention of the premature shutoff of protein synthesis in the infected host. Initially designed for the treatment of central nervous system tumors, recombinant replication-competent HSV-1 mutants are emerging as potent oncolytic agents. Clinical trials are currently investigating intracerebral tumor administration of such ICP34.5-negative mutants for the treatment of malignant gliomas. However, a continuously expanding list of tumors are proving sensitive to HSV oncolysis, including ovarian cancer, breast cancer, prostate cancer, mesothelioma, malignant melanoma, metastatic colon carcinoma, and head and neck squamous carcinomas. In animal studies, we could not document any spread of the virus beyond the intraperitoneal tumors by immunohistochemistry or polymerase chain reaction following intraperitoneal administration of the virus, and no toxicity was seen. A growing bulk of evidence suggests that HSV-based oncolytic therapy may represent a safe tool for the treatment of solid tumors (Table 5).

Epithelial ovarian cancer cells are highly susceptible to infection and killing by recombinant HSV-1. Notably, primary cultures were significantly more susceptible to HSV killing than established lines. Furthermore, HSV-1 lacking ICP34.5 is equally efficient in chemotherapy-sensitive and -resistant epithelial ovarian cancer cells in vitro and in vivo. Epithelial ovarian cancer cells were found to undergo varying degrees of apoptosis, depending on the cell line. Apoptosis was not dependent on the p53 status of the cells, which may partially account for the fact that chemotherapy resistance does not affect the sensitivity of epithelial ovarian cancer cells to HSV oncolysis. We further investigated the tumor specificity of HSV-G207, a doubly deleted HSV-1 lacking ICP34.5 and ribonucleotide reductase that regulates viral proliferation. HSV-G207 induced a dose-dependent lysis in epithelial ovarian cancer cells in vitro but spared normal human mesothelial cells. ONYX-15 Oncolytic HSV-1 appears promising and warrants testing in epithelial ovarian cancer.

**ONYX-15**

Another oncolytic agent of potential interest is the E1B-defective adenovirus ONYX-015. Adenoviral E1B gene encodes a 55-kd protein that inactivates the p53 tumor-suppressor gene. The initial speculation that p53 inhibits adenoviral replication prompted the engineering of a recombinant...
adenovirus lacking E1B. It was anticipated that this virus would replicate in p53-deficient tumor cells but not in cells possessing wild-type p53, and great enthusiasm was generated by the observation that this was, in fact, true. Intratumoral injection of ONYX-015 into human cervical carcinoma (where p53 is rapidly degraded due to the presence of human papillomavirus E6 protein product) grown in nude mice led to complete regression in 60% of the tumors.[44] Further reports confirmed that intratumoral or intravenous administration of ONYX-015 to nude mice bearing human xenografts from a variety of tumors had antitumoral efficacy and that the virus was not toxic to normal human cells. Moreover, a synergism with platinum-based chemotherapy was seen. However, conflicting results were obtained by different authors who reported that intact p53 function and p53-dependent apoptosis were necessary for adenoviral replication.[45] Clinical trials of ONYX-015 in head and neck cancer and lung cancer are ongoing. In spite of the controversy surrounding the mechanism of action and tumor selectivity of ONYX-015, preliminary results from a phase II study of ONYX-015 plus fluorouracil/cisplatin chemotherapy in 30 head and neck cancer patients indicated extremely promising results. There were substantial and persistent objective responses, including a high proportion of complete responses.[46] A randomized phase III trial currently under preparation in head and neck cancer will further clarify the efficacy of ONYX-015. Because epithelial ovarian cancer patients often display mutations in p53, ONYX-015 may be useful in the treatment of recurrent/persistent epithelial ovarian cancer.

Conclusions

Gene and oncolytic therapy of ovarian cancer is an intense area of investigation. Significant focus is being placed on the development of vectors that yield improved gene transfer with low toxicity. As our understanding of tumor cell biology, tumor immunology, and tumor angiogenesis increases, it is likely that new molecular targets will be incorporated into cancer gene therapy strategies in an attempt to enhance tumor cell death, generate potent antitumor immune responses, and suppress angiogenesis. The existing clinical evidence suggests that these techniques are probably best suited for patients with a minimal volume of residual disease. It is likely that multimodality approaches with conventional strategies (eg, cytoreductive surgery, chemotherapy, radiation therapy) and novel therapeutic tools including oncolytic, gene, angiostatic, and immune therapy, in various combinations will prove advantageous, compared to single-modality treatments. Multicenter, prospective double-blinded studies need to be designed to test these hypotheses.

References:


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