Scientific Abstract

Phase I Trial of Intraperitoneal Administration of an Attenuated Strain (Edmonston Strain) of Measles Virus, Genetically Engineered to Produce CEA, in Patients with Recurrent Ovarian Cancer

Ovarian cancer is the second most common malignancy of the female genital tract in the United States. There are an estimated 25,400 new cases of ovarian cancer a year and over 14,500 deaths. Most patients (more than 70%) present with advanced disease that has spread beyond the ovaries, and the majority of these patients will relapse after initial treatment with surgery followed by a platinum/taxane chemotherapy regimen. The available salvage treatment for recurrent disease consists of chemotherapy which can lead to responses in the minority of patients (6-14% of patients with platinum refractory disease), and most patients will subsequently progress in a few to several months. There is an urgent need for innovative approaches for the treatment of advanced disease. Given the fact that, in more than 85% of patients ovarian cancer remains confined in the peritoneal cavity, makes it an attractive target for intraperitoneal administration of therapeutic agents. In our laboratories, we have created a recombinant attenuated Edmonston vaccine strain of measles virus (MV-CEA) that expresses the inert soluble marker peptide, human carcinoembryonic antigen (CEA). The rationale for the construction of this attenuated vaccine strain of measles virus has been the antitumor activity of several viruses of the Paramyxovirus family in which the measles virus belongs. Furthermore, and in contrast to wild-type measles virus, vaccine strains of measles virus have an excellent safety record after millions of doses having been administered worldwide. Engineering of the attenuated Edmonston vaccine strain to produce CEA allows us to monitor viral gene expression by following serum levels of CEA and, therefore, individualize the treatment in order to achieve optimal safety and efficacy without a need for invasive procedures. MV-CEA showed significant antitumor activity in a variety of commercially available and patient-derived ovarian cancer cell lines and tumor xenografts, both in a subcutaneous as well as an orthotopic SKOV3ip.l ovarian cancer model. In contrast, it caused minimal cytopathic effect in normal ovarian surface epithelial cells and mesothelial cells.

We propose exploring the use of MV-CEA in a phase I dose-escalation trial for patients with recurrent ovarian cancer. Study objectives are (1) to determine the safety and toxicity of intraperitoneal administration of MV-CEA in patients with recurrent ovarian cancer, (2) to determine the maximally tolerated dose of MV-CEA administered intraperitoneally, (3) to characterize viral gene expression at each dose level as manifested by CEA titers, (4) to assess viremia, viral replication, and shedding/persistence of MV-CEA following intraperitoneal administration, (5) to determine humoral and cellular immune response to the injected virus, and (6) to assess, in a preliminary fashion, antitumor efficacy. The virus will be administered in escalating doses from 10^3 pfu to 10^9 pfu via a peritoneal catheter and repeat administration every four weeks for up to six cycles is planned, provided that there is no progression, no evidence of viremia, and the patients' DTH has returned to more than 75% of baseline at the time of retreatment. Patients will be followed by both imaging and the tumor marker

CA-125. Extensive correlative studies are also proposed: Patients' peripheral blood mononuclear cells will be tested for viremia. In addition, patients' urine and throat swabs will be tested for viral shedding. Peritoneal aspirates will be tested for viral presence by (a) QRT-PCR, (b) co-culture with Vero cells, and (c) *in situ* hybridization for the presence of measles virus nucleocapsid N-mRNA. CEA titers and anti-measles virus antibodies will be measured in the serum and peritoneal aspirates at different time points. Up to 22 patients will be enrolled for the phase I part of the study with another 12 patients being enrolled at the phase II dose once MTD has been determined in order to accomplish a preliminary assessment of efficacy.