

1. SCIENTIFIC ABSTRACT

The identification of unique tumor-associated antigens capable of eliciting cytotoxic T-lymphocyte (CTL) responses has led to new methods of immunotherapy for cancer. One method is the insertion of a tumor antigen cDNA clone into a live virus that can be used in active immunization protocols. This approach was used to generate a vaccinia virus that expressed the human carcinoembryonic antigen (CEA) gene. Vaccinia was chosen as a vector because of its ability to accept a large amount of foreign DNA, its replicative stability, its ability to generate strong CD8⁺ CTL responses, and its success as an immunizing agent in the smallpox eradication program. The recombinant vaccinia-CEA virus (rV-CEA) was shown to have therapeutic effectiveness in the prophylaxis and treatment of an established CEA-expressing murine adenocarcinoma tumor. Furthermore the construct elicited both anti-CEA antibodies and CTL directed against CEA in mice. The vaccine induced similar immune responses in a non-human primate model and was shown to be safe with few side effects.

The FDA and RAC granted permission to perform a clinical trial in human patients with this vaccine in 1992. Two simultaneous clinical trials were performed in patients with metastatic cancer whose tumor expressed CEA. Results of these studies revealed that patients could tolerate the highest doses of vaccinia with few toxic side effects. Immunological monitoring led to the identification of two CEA-specific epitopes that induced CTL in an HLA-A2-restricted manner. Immune assays also showed that only a single dose of vaccinia could elicit a strong immune response as evidenced by the local skin reaction and induction of anti-vaccinia CTL. This is presumably because of retained memory following the initial vaccination. This problem has led to the design of other pox viruses that are highly attenuated in humans, such as NYVAC and fowlpox viruses, such as ALVAC. These viruses are replication-deficient in mammalian cells and do not result in lytic infection as vaccinia virus does. However, the viruses are capable of presenting antigen and inducing immune responses to cloned antigens. These viruses are thought to be more likely to induce immunity because of a weaker memory response and have the added advantage of decreased pathogenicity because they are replication-incompetent in mammalian cells.

Further animal data has indicated that anti-tumor responses to recombinant pox viruses can be enhanced by the addition of the costimulatory molecule B7 into the viral genome. Increased CTL responses against model tumor antigens have been identified when B7 is added to the viral genome. These findings led to the development of a recombinant ALVAC virus expressing both the CEA and B7 genes. This construct was developed by the Laboratory of Tumor Immunology and Biology at the National Cancer Institute and has not previously been tested in human patients. The basic premise of this trial is to determine the safety and immunogenicity of this novel construct. Patients with CEA-expressing colorectal adenocarcinomas who meet the eligibility criteria will be enrolled and peripheral blood samples will be collected from pre- and post-treatment analysis of antigen-specific responsiveness. The use of CEA and B7 is unique and may provide a more powerful immune response with the possibility of clinical and/or pathologic responses. These measurements will also be obtained. This study should establish the safety, dosing, toxicity profile, and immunological responses to this unique recombinant ALVAC-CEA-B7 vaccine.