

2. NON-TECHNICAL ABSTRACT

While recent advances in chemotherapy have shown that new combination regimens can improve survival of patients with metastatic colorectal cancer, there is no cure for this disease. For patients that have progressed on chemotherapy, the prognosis is poor, and clinical trials are needed to test new agents in this setting. The ability for vaccines to stimulate an immune response against cancer cells depends on the activity of specific T-cells, which can recognize a particular protein, or antigen, found on the tumor cells. These T-cells can be generated by immunization with poxviruses that contain the genes for the tumor proteins. Two of the most commonly found proteins in colorectal tumor cells are carcinoembryonic antigen (or CEA) and a mucin protein called MUC-1. Vaccinia virus is the vaccine used to prevent smallpox and has been used to produce both CEA and MUC-1 previously. Fowlpox virus is a virus that infects birds but does not cause disease in humans and has also been used to produce the CEA protein. These vaccines have been tested in humans with cancer and appear to be safe after being given to over 600 people in clinical trials. The T-cells also require a second signal to become fully activated, which are provided by specialized immune system proteins called co-stimulatory molecules. There are many co-stimulatory molecules that have been discovered and can be used to help activate T-cells. A new vaccine has been developed using vaccinia virus to express CEA and three co-stimulatory molecules (called B7.1, ICAM-1, and LFA-3), called rV-CEA(6D)/TRICOM. A vaccinia virus that produces MUC-1 has also been generated (called rV-MUC-1) and there is some evidence that using two different proteins may improve the responses to a vaccine approach. In addition, a new fowlpox virus was also made with the human CEA and three co-stimulatory molecule genes, and called rF-CEA(6D)/TRICOM. Animal studies and at least two human clinical trials have suggested that the use of two different vaccines, such as vaccinia followed by fowlpox virus, are better than using a single virus vaccine. Granulocyte-macrophage colony stimulating factor (GM-CSF) is a protein of the immune system that is approved for use in humans to increase the number of white blood cells and has also shown some promise as an anti-cancer agent, especially when used in combination with vaccines. The goal of this study is to determine whether rV-CEA(6D)/TRICOM mixed with rV-MUC-1 followed by rF-CEA(6D)/TRICOM in combination with GM-CSF is safe and can start an immune response against CEA and MUC-1 on the colorectal tumor cells.