

Scientific abstract

Treatment of patients with advanced epithelial ovarian cancer using anti-CD3 stimulated peripheral blood lymphocytes transduced with a gene encoding a chimeric T-cell receptor reactive with folate binding protein

Ovarian cancer is the leading cause of gynecologic cancer death in the United States, and is the fourth most frequent cause of cancer death in women. There are over 24,000 new cases of ovarian cancer annually in the U.S., resulting in 13,600 deaths. Because ovarian cancer is usually asymptomatic until metastases occur, patients present with advanced disease in more than two-thirds of cases. Although platinum-based chemotherapies result in significant response rates, treatment results in prolonged disease-free intervals without a significant impact on ultimate survival.

Adoptive immunotherapies using tumor infiltrating lymphocytes and interleukin-2 have been developed for some cancers. These therapies have resulted in significant long-term responses in some patients with melanoma. Translating these T-cell based therapies to other types of cancer has been difficult.

In an effort to broaden the applicability of adoptive immunotherapy to common cancers, such as ovarian, breast and colon cancer, we have developed an approach to cancer treatment that redirects the immune reactivity of lymphocytes to antigens recognized by monoclonal antibodies. To do this, we use a retroviral vector that encodes chimeric receptor genes consisting of the variable regions of a monoclonal antibody (mAb) joined to the transmembranous and cytoplasmic domains of a T-cell receptor (TCR) signaling chain. Our initial studies have utilized a chimeric receptor gene derived from an anti-ovarian cancer mAb, MOv18. TIL or anti-CD3 stimulated peripheral blood lymphocytes (PBL), retrovirally transduced with the MOv18 chimeric receptor gene (MOv- γ), could specifically lyse and produce cytokine upon coculture with human ovarian cancer cells.

In addition, TIL transduced with the MOv18-derived chimeric receptor (MOv TIL) have been shown to function in vivo in murine models. Nude mice implanted intraperitoneally with human ovarian cancer cells (IGROV) were treated 3 days later intraperitoneally with gene-modified murine TIL, derived from an unrelated murine tumor. Mice treated with MOv-TIL had significantly increased survival compared to mice treated with saline only, nontransduced TIL or TIL transduced with an irrelevant receptor (TNP-TIL). In another murine model, intravenously administered MOv-TIL were capable of significantly reducing lung metastases from a tumor bearing the MOv18-defined antigen.

These studies indicated that primary lymphocytes could be stably genetically modified to be redirected in vitro and in vivo against new antigens, defined by monoclonal antibodies. We thus propose to treat patients with recurrent, evaluable ovarian cancer with intravenously administered autologous MOv-PBL and IL-2, and to treat patients with minimal residual disease with intraperitoneally administered autologous MOv-PBL and IL-2. This clinical trial will help determine the safety and efficacy of this approach, which potentially could be applicable to a number of neoplastic and infectious processes, enabling adoptive immunotherapy to be used to treat diseases not previously amenable to this treatment modality.