

SCIENTIFIC ABSTRACT

High Dose chemotherapy (HDCT) and autologous bone marrow transplantation (BMT) is frequently used to treat patients with metastatic cancer including breast cancer and neuroblastoma. However, the bone marrow of such patients is often contaminated with tumor cells. Recently, we have found that a recombinant adenovirus vector that contains a *bcl-x_s* minigene (a dominant negative inhibitor of the *bcl-2* family), called the *bcl-x_s* adenovirus, is lethal to cancer cells derived from epithelial tissues, but not to normal human hematopoietic cells. To determine the mechanism, by which this virus spares normal hematopoietic cells, we isolated normal mouse hematopoietic stem cells and infected them with an adenovirus that contains a β -galactosidase minigene. Such cells do not express β -galactosidase, indicating that hematopoietic stem cells do not express transgene encoded by adenovirus vectors based upon the RSV-AD5 vector system. When breast cancer cells mixed with hematopoietic cells were infected with the *bcl-x_s* adenovirus, cancer cells were selectively killed by the suicide adenoviruses. Hematopoietic cells exposed to the suicide vectors were able to reconstitute the bone marrow of mice exposed to lethal doses of γ -irradiation. These studies suggest that adenovirus suicide vectors may provide a simple and effective method to selectively eliminate cancer cells derived from epithelial tissue that contaminate bone marrow to be used for autologous BMT. We therefore propose to initiate a phase I clinical trial to test the safety of this virus in women with breast cancer undergoing high does chemotherapy and autologous BMT.