

Scientific Abstract

Osteosarcomas are malignant tumors arising from skeletal tissue and occur most frequently during childhood and adolescence. Osteosarcoma was once fatal in more than 80% of patients who presented with apparently localized disease. Chemotherapy, better surgical techniques and improved staging methods now allow most patients to be treated with limb sparing surgery and to be cured of their disease. However, many patients still die of metastatic disease and new approaches are still needed. The lung is the most frequent metastatic site and is treated with chemotherapy and surgical resections. Multiple resections for repeated recurrences that are limited to the lung are not uncommon but are limited by the amount of lung tissue that can be removed and become futile as recurrences become more frequent. Although a main component of initial therapy, chemotherapy has not been shown to be of benefit for recurrent disease.

Direct introduction of therapeutic genes into malignant cells *in vivo* may provide effective treatment of solid tumors. The proposed study will use the adenoviral vector Ad-OC-E1a (OCap1), which contains a murine osteocalcin (OC) promoter to regulate the production of the adenoviral E1a protein to allow for restricted viral replication and subsequent lysis of tumor cells. The OC promoter is developmentally regulated, with peak expression in the neonate. It functions primarily in osteoblasts found in growing bone and is highly expressed in osteogenic sarcomas. Because adenovirus is quickly cleared by normal tissues, especially the liver, systemic administration has been problematic. Although bioavailability would be decreased following exposure to the liver, the OCap1 construct should not be hepatotoxic due to OC-restricted tissue expression of the E1a protein. Metastatic disease to the lung is a major problem and often is the cause of death for patients with osteogenic sarcoma. Treatment of pulmonary metastases could potentially be accomplished using intravenously administered OCap1 since the material would pass through the lung prior to reaching the systemic circulation. In animal models using OC expressing tumors, OCap1 has been effective at reducing lung metastases following intravenous injection.

This protocol is a phase I/II investigational study of bolus intravenous injections of Ad-OC-E1a for the treatment of chemotherapy refractory osteogenic sarcoma that has metastasized to the lungs. Initially patients will receive one injection of 1×10^{10} , 1×10^{11} , 1×10^{12} , or 5×10^{12} viral particles of Ad-OC-E1a using a standard Phase I dose escalation design that studies 3 to 6 patients per dose group. After safety has been established in the first part of the trial, we will evaluate the anti-tumor activity of Ocap1. Because the matrix associated with osteogenic sarcoma may not change despite tumor necrosis, radiographic evaluation alone has not been considered sufficient to evaluate response in this disease. Histologic criteria that assess the amount of necrosis have been shown to have prognostic significance and are a key component of the anti-tumor response assessment. Therefore the anti-tumor assessments will be carried out in patients for whom resection of their pulmonary metastases is clinically indicated. These patients will receive one injection of Ocap1 and 28 to 42 days later undergo their planned pulmonary resection. Responses will be graded using radiographic and histologic objective response criteria that are considered standard for osteogenic sarcoma. A total of 14 to 25 patients, depending upon whether objective anti-tumor responses occur, will be studied in this part of the protocol.