HSV-TK Gene Therapy Promising in Prostate Cancer

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LOS ANGELES--Preliminary results with a gene-therapy approach to recurrent prostate cancer suggest antitumor activity in at least some patients. Three of 18 patients have had decreases in PSA levels of more than 50%. The effects have persisted for 45 to 290 days, including one patient who became biopsy negative for a brief period of time.

"The results suggest this is a real response, not a transient episode related to inflammation," Peter Scardino, MD, chairman of urology, Baylor College of Medicine, Houston, said at an ASCO integrated symposium on prostate cancer.

For the past 3 years, the Baylor group has evaluated the therapeutic potential of the herpes simplex virus-thymidine kinase (HSV-TK) gene delivered to prostate cancer cells by a replication-deficient adenoviral vector, followed by IV ganciclovir (Cytovene). Preclinical studies showed that the HSV-TK gene penetrated 10% to 15% of cells in culture but induced a cell-killing rate of about 99% because of a profound "bystander effect" in surrounding tumor cells, he said.

Clinical investigation began last year. All patients selected for the initial safety trial had biopsy-proven recurrence after primary radiotherapy for clinically localized disease. The patients had rising PSA levels but no evidence of metastases. None had received hormonal therapy. "We selected these patients for the trial because currently there is no standard treatment for this group," Dr. Scardino said.

Intralesional injection of the HSV-TK gene complex began at a dose of $1 \times 10^8$ IU, and ganciclovir was given at an IV dose of 5 mg/kg twice a day for 2 weeks. This dose caused "absolutely no evidence of toxicity" but also had no apparent effect on tumors, Dr. Scardino said. Thus, he requested and received permission from the FDA to increase the HSV-TK dosage until toxicity did appear.

Dr. Scardino said that 18 patients have received the HSV-TK gene at doses ranging from $1 \times 10^8$ to $1 \times 10^{11}$ IU. Three patients have had what the investigators interpret as responses to the therapy. The first response occurred in a patient who received $1 \times 10^9$ IU of HSV-TK. One response occurred at $1 \times 10^{10}$, and the third at $1 \times 10^{11}$. Response was defined as a PSA decline of 50% or more. One patient temporarily became biopsy negative, and biopsy specimens revealed a marked evidence of tumor necrosis.

Toxicity has been minimal in the ongoing trial. Principal side effects have included chills and fever. One patient developed grade IV toxicity in the form of thrombocytopenia and abnormal liver function. The platelet count dropped to 10,000 in this patient, necessitating platelet transfusion. No evidence of viral shedding from the adenoviral vector has appeared in cultures or in blood. The vector did appear in the urine of eight patients, and in a semen sample in the one patient who could provide semen. Two patients had low levels of antiadenoviral antibodies. Continuation of the phase I trial will test the safety of a second injection of the HSV-TK gene and injection of multiple tumor sites. "In the future, I think there is an opportunity to look at combinations involving gene therapy and androgen ablation in patients who are going to be treated with radiotherapy," Dr. Scardino said. "We already have excellent results of combination therapy in animal models of prostate cancer."

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