MedicalXpress

Researchers pioneer new approach to treating HPV-related cervical cancer

November 20 2014

A drug that is already well established as a treatment for infection of the retina in people with AIDS has been shown, for the first time, to sensitise cervical cancer to chemotherapy and radiotherapy without an increase in toxic side-effects.

Cidofovir is an anti-viral drug that is effective against several viruses, including the human papilloma virus (HPV), which is implicated in the onset of cervical cancer. It targets the cancer-causing proteins (oncoproteins) produced by HPV. These oncoproteins interfere with the action of other proteins that control genome stability and cell death, and so, when cells are infected with HPV they become resistant to dying. However, preclinical work by researchers in France has shown that cidofovir stops the activity of the HPV-related oncoproteins, leading to a restoration of "pro death" proteins such as p53. This means that when the cervical cancer cells are targeted with chemotherapy and radiotherapy (chemoradiation), they are more likely to die.

Professor Eric Deutsch, professor of radiation oncology and head of the radiation oncology department and research unit at the Institut Gustave Roussy, Villejuif, France, will tell the 26th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics in Barcelona, Spain, today (Thursday) that although cidofovir was approved as a stand alone therapy for infectious disease, until now it was unknown whether it was safe to use it in combination with chemoradiation.

"As a result of the findings from our preclinical studies, we have

conducted what is, to my knowledge, the first phase I clinical trial in cervical cancer patients, using cidofovir to target the HPV oncoproteins in combination with chemoradiation," he will tell the meeting. "The major finding from the trial is that cidofovir did not increase the toxicity or worsen the tolerability of chemoradiation. We also found that the combination resulted in tumour shrinkage in all the patients who could be evaluated in the trial, with a complete response, in which the tumours disappeared for a time, in 80% of these patients.

"The fact that the combination of cidofovir and chemoradiation did not lead to an increase in toxic side-effects is a crucial finding because the women in our trial had locally advanced cervical cancer that had not spread to the rest of the body - unlike many other phase I trials that test new treatments in very ill patients with metastatic cancer that has failed to respond to several previous therapies. So, for the women in our trial, any increase in toxic side-effects or a worsening of the tolerability of the treatment would have been unacceptable."

Fifteen women joined the trial and received injections of cidofovir at doses ranging from 1-6.5mg per kilogram of body weight weekly for two weeks, and then every two weeks from the start of chemoradiation (45Gy radiotherapy delivered to the pelvis and intravenous weekly carboplatin) until the start of brachytherapy in the uterus and vagina. The women received a total of six injections of cidofovir and the median duration of therapy was ten weeks. Results from all 15 women were available for evaluation at the time of the Barcelona meeting.

One of the major dose-limiting side-effects of cidofovir is permanent kidney damage. However, none was seen in this trial. Two of the six patients receiving the maximum dose of 6.5mg per kilogram of body weight suffered dose-limiting toxicities. One patient presented with febrile neutropenia (deficiency of infection-fighting white blood cells called neutrophils) and renal infection associated with bacteraemia

(bacteria in the blood). Another patient developed transient proteinuria (an excess of protein in the urine); of interest, recovery of normal renal function was seen in this patient. Most of the other side-effects observed in other patients were relatively limited in intensity and are observed with the standard chemoradiotherapy regimen without cidofovir.

There was no evidence that the treatment increased the tumours' resistance to radiation treatment.

The recommended dose for a phase II trial is 5mg per kilogram of body weight, and the researchers hope to start a phase II/III trial soon in order to quantify precisely how the combination benefits patients in terms of controlling the cancer and extending overall survival.

"The results from this phase I trial show that the combination of cidofovir with chemoradiation is a new, targeted anti-cancer approach, which enables us to target cancer cells specifically with a limited impact on healthy tissues, thereby avoiding unacceptable adverse side-effects," Prof Deutsch will say.

"HPV-related cancers, such as cervical cancer, are extremely common worldwide. If we consider the treatment of cervical cancer in lower income countries, such as those in South America, Asia, Africa and Eastern Europe, our approach should be relatively inexpensive because cidofovir has been known for years and is available off patent.

"This is also why it has taken us more than ten years to move from the first preclinical data to a phase I trial. Due to lack of interest and support from the pharmaceutical industry, the trial had to be performed with 100% academic funding."

Dr Lee Helman, a member of the scientific committee for the EORTC-NCI-AACR Symposium and scientific director for the Clinical Research

Center for Cancer Research at the NCI, who was not involved with the study, commented: "The application of the anti-viral drug, cidofovir, to chemo-radiation treatment in cervical cancer is a logical extension of our understanding of the role of the HPV virus in this tumour. It has been demonstrated that HPV, in part, transforms cells through interference with the p53 protein, often called the 'guardian of the genome'. These investigators hypothesised that the ability of cidofovir to suppress HPV virus could potentially enhance the response of cervical cancer to DNA-damaging treatment consisting of radiation and chemotherapy. This study demonstrates the feasibility of this approach and paves the way for a definitive study to test the advantage of adding cidofovir to standard chemo-radiation therapy in cervical cancer."

Provided by ECCO-the European CanCer Organisation