MedicalXpress

Clinical trials designed to block autophagy in multiple cancers show promise

May 22 2014

In the largest group of results to date, researchers from Penn Medicine's Abramson Cancer Center and other institutions have shown in clinical trials that the malaria drug hydroxychloroquine (HCQ) blocked autophagy in a host of aggressive cancers—glioblastoma, melanoma, lymphoma and myeloma, renal and colon cancers—and in some cases helped stabilize disease. Autophagy—an essential process cancer cells need to fuel their growth—is a key troublemaker spurring tumor growth. Block this pathway, many preclinical studies suggest, and anti-cancer agents such as chemotherapy and radiation therapy will be able to do their job better.

Results of six trials—five in humans (with over 200 patients) and one in dogs—are all reported in the May online issue of *Autophagy*, and will be presented at the Keystone Symposia on Autophagy in Austin, Texas, on Monday, May 26, by author Ravi K. Amaravadi, MD, assistant professor of Medicine in the division of Hematology/Oncology at the Perelman School of Medicine and co-leader of the Cancer Therapeutics Program at Penn Medicine's Abramson Cancer Center, who was the principal investigator on four of the six trials, which included a multi-disciplinary team of investigators at Penn Medicine and other institutions treating a wide range of cancers.

"There are currently over 40 clinical trials involving HCQ as a potential autophagy inhibitor worldwide, and the results of our trials are among the first to be published," said Amaravadi. "These studies provide promising evidence that autophagy blockade can be achieved, and that

combining autophagy inhibitors with other cancer therapies in very sick patients can be accomplished safely in most cases. We wanted to present the data for all of these trials at one time, because when presented side by side, a more comprehensive and synergistic understanding of the potential of blocking this pathway emerges."

The phase I and phase I/II trials aimed to measure the safety of adding HCQ to either chemotherapy, radiation therapy or targeted therapies, its effectiveness at inhibiting autophagy, and the potential clinical benefit of HCQ combination therapies.

In melanoma, researchers observed prolonged stable disease in 20 percent of the patients on temozolomide. While in another trial, researchers observed stable disease in 75 percent of patients with metastatic melanoma on temsirolimus. In the dog clinical trial, all 30 dogs with non-Hodgkin's lymphoma treated with HCQ and the standard chemotherapy doxorubicin had clinical benefit, and nine had complete remission.

Autophagy is a relatively new target in cancer, infectious disease and neurodegenerative disorders, and while advances in the fundamental understanding of autophagy are increasing at a breakneck speed, translation of these advances into clinical trials and clinical benefit has been lagging. More recently, HCQ has shown promise in treating pancreatic cancer patients in ongoing clinical trials; however, its tolerability and effectiveness to stop autophagy in humans with other cancers has not been shown before.

The following is a brief summary of each of the six clinical trials, which can be found here.

Trial #1: A phase I/II trial of HCQ in conjunction with radiation therapy and concurrent and adjuvant temozolomide in patients with newly

diagnosed glioblastoma multiforme

These data from a national trial with 92 glioblastoma patients established that autophagy inhibition is achievable with HCQ; however, toxicity prevented escalation to higher doses. Therefore, a definitive test of the role of autophagy inhibition in the adjuvant setting for glioma patients awaits the development of lower-toxicity compounds for optimal inhibition. No significant improvement in overall survival was observed.

Trial #2: Phase I trial of HCQ with dose-intense temozolomide in patients with advanced solid tumors and melanoma

A trial with 40 patients (73 percent with metastatic melanoma) showed that high-dose HCQ and the oral chemotherapy drug temozolomide is safe and tolerable, and is associated with autophagy inhibition. Prolonged stable disease and responses observed in about 20 percent of the patients suggests antitumor activity.

Trial #3: Combined autophagy and proteasome inhibition: A phase 1 trial of HCQ and bortezomib in patients with relapsed/refractory myeloma

A phase I trial with 25 patients combining bortezomib and HCQ for relapsed or refractory myeloma achieved autophagy inhibition and was tolerated. Of 22 patients evaluable for response, 3 (14 percent) had very good partial responses, 3 (14 percent) had minor responses, and 10 (45 percent) had a period of stable disease.

Trial #4: Combined mTOR and autophagy inhibition: Phase I trial of HCQ and temsirolimus in patients with advanced solid tumors and melanoma

This study of 27 patients indicates that temsirolimus, an mTOR

inhibitor, and HCQ is safe and tolerable, blocks autophagy, and had significant antitumor activity; researchers observed stable disease in 75 percent of those patients with metastatic melanoma.

Trial #5: Combined autophagy and HDAC inhibition: A phase I safety, tolerability, pharmacokinetic, and pharmacodynamic analysis of HCQ in combination with the HDAC inhibitor vorinostat in patients with advanced solid tumor.

A phase I clinical trial conducted by investigators at the University of Texas San Antonio, showed that the combination of HCQ and the chemotherapy drug vorinostat in 27 patients with advanced solid tumors, including renal cell carcinoma and colon cancer, was clinically safe and inhibited autophagy. What's more, one patient who had failed multiple prior treatments for renal cell carcinoma had a confirmed durable partial response and two patients with colorectal cancer had prolonged stable disease.

Trial #6: Phase I clinical trial and pharmacodynamic evaluation of combination HCQ and doxorubicin treatment in pet dogs treated for spontaneously occurring lymphoma

A phase I trial conducted by investigators at the Colorado State University Veterinary School in 30 dogs with non-Hodgkin's lymphoma with HCQ and the standard chemotherapy doxorubicin (DOX) showed a 100 percent clinical benefit rate. Nine of the dogs had complete remission. These results are encouraging given that reported response rates with DOX alone for treatment-naive lymphoma in dogs range from 60-85 percent. The tissue samples provided by the dogs provided valuable information about HCQ pharmacology and demonstrated that clinical trials in dogs can not only benefit pets, but can advance scientific knowledge.

"The promising safety results of these early trials set the stage for additional HCQ trials in different cancers, and trials involving new autophagy inhibitors that are being developed by pharmaceutical companies," said Amaravadi. "However, more work needs to be done before we can declare HCQ as a viable and cost-effective drug to help improve the efficacy of certain anti-cancer agents for the treatment of many cancers.

"If we can find the type of cancer patients for whom this approach works best, it could have a huge impact for global cancer care. In the meanwhile, cancer patients should only be treated with new HCQ combinations in the setting of a clinical trial."

Provided by University of Pennsylvania School of Medicine