

Modern targeted drug plus old malaria pill serve a 1-2 punch in advanced cancer patients

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Researchers at the University of Pennsylvania School of Medicine may have found a way to turn an adaptive cellular response into a liability for cancer cells. When normal cells are starved for food, they chew up existing proteins and membranes to stay alive. Cancer cells have corrupted that process, called autophagy, using it to survive when they run out of nutrients and to evade death after damage from chemotherapy and other sources. When the Penn investigators treated a group of patients with several different types of advanced cancers with temsirolimus, a molecularly targeted cancer drug that blocks nutrient uptake, plus hydroxychloroquine, an anti-malarial drug that inhibits autophagy, they saw that tumors stopped growing in two-thirds of the patients.

Amaravadi's team will present the data at the [American Association for Cancer Research](#) 102nd Annual Meeting 2011 in Orlando on Tuesday, April 5.

"The results are very encouraging -- striking, even" says senior author Ravi Amaravadi, MD, an assistant professor of Medicine at Penn's Abramson Cancer Center. "Temsirrolimus by itself has little effect in this patient population. Tumors laugh at it, with response percentages of just zero to 5 percent. But by combining it with hydroxychloroquine, we found that 14 out of 21 patients had stable disease after treatment, including five out of six melanoma patients."

In addition to melanoma, patients involved in the study also had

colorectal, head and neck, breast, gastro-esophageal, prostate, pancreatic, lung and adrenal cancers. Not only did patients show substantial rates of disease stabilization with the treatment combination, but the researchers report that side effects observed were relatively limited; most commonly mouth sores, weight loss, nausea, and fatigue. Two patients developed infections when the large tumors they had at the start of the trial caved in on themselves as treatment killed off the internal [cancer cells](#), but both patients responded to antibiotics and were able to remain on the study regimen.

Amaravadi's group was able to see evidence of autophagy inhibition in peripheral blood cells in patients treated with the combination. And the inhibition increased with increasing doses of hydroxychloroquine, suggesting that the drug is working as they hypothesized it would.

More serious side effects, including low blood cell counts, in a previous phase I trial that combined hydroxychloroquine with chemotherapy and radiation. "That was unexpected and shows that hydroxychloroquine is an experimental drug, even though it has been approved for other treatments for many years," he says. "We didn't see that problem in this trial, so our findings show that what you combine it with is critical — and some combinations will be less tolerable."

The researchers note that the relatively limited side effect profile of the novel temsirolimus-hydroxychloroquine combination suggests researchers may be able to layer other therapies on top of it, making the combination an even more powerful treatment.

Given the large proportion of [melanoma](#) patients who benefited from this combination in the initial cohort of patients, the investigators are currently enrolling an additional 12 patients in an expansion cohort at the 1200 mg dose of hydroxychloroquine. They are also hopeful that the drug combination will also be useful in patients with head and neck and

breast cancers.

Provided by University of Pennsylvania School of Medicine

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