

Clinical trial suggests new direction for heavy-smoking head and neck cancer patients

August 14 2018, by Garth Sundem

Patients with a greater than 10 pack/year history of smoking tend to develop an especially dangerous form of head and neck squamous cell cancer (HNSCC) for which prognosis remains poor and treatments have changed little during the past two decades. However, recent phase 1 clinical trial results by the Head and Neck Cancer Group at University of Colorado Cancer Center suggest a possible new direction for these patients. The first-in-human trial of the oral PARP inhibitor olaparib, with the anti-EGFR drug cetuximab and radiation, led to 72 percent 2-year survival in 16 patients on trial, compared with an expected 2-year survival rate of about 55 percent for standard-of-care treatment.

"Colorado promotes innovation, and this trial was certainly innovative when it was designed by our group," says David Raben, MD, CU Cancer Center investigator and professor in the CU School of Medicine Department of Radiation Oncology. "Much credit goes to Antonio Jimeno, MD, Ph.D. who was very supportive of this idea and helped move this forward along with Dr. Sana Karam and Dr. Daniel Bowles."

The drug cetuximab targets EGF receptor signaling (EGFR) and while it earned FDA approval in 2006 for use against head and neck cancers over-expressing EGFR, Raben stated there is significant room for improvement.

"That's where olaparib and radiation come in," he says. "Ten years ago, I was on a sabbatical from CU, working for AstraZeneca in England. And I remember taking the train from Manchester to Cambridge to learn

about this new drug from a small biotech company called Kudos Pharmaceuticals. It was a PARP-inhibitor, meant to keep cells from repairing damaged DNA. That's the drug we now call olaparib."

Early in development, the drug had shown remarkable activity in woman with BRCA mutations, "but we wanted to know if it worked in other diseases where BRCA wasn't the story," Raben says.

Olaparib inhibits the action of an enzyme known as PARP, which is important for DNA repair. HNSCC in heavy smokers already tends to carry a heavy load of DNA damage. And radiation creates additional DNA damage. When olaparib nixes the ability of these cancers' to repair DNA, it can push [cancer](#) cells past the tipping point of damage and into cell death. In this way, PARP inhibition and radiation may be synthetically lethal, meaning that together they exploit deficiencies in gene defects that leads to enhanced cell death.

In fact, lab work by Raben and CU Cancer Center colleagues including Xiao-Jing Wang MD, Ph.D., Barb Frederick, Ph.D., and Ariel Hernandez, among others, shows that PARP inhibitors like olaparib may also amplify the effects of anti-EGFR drugs like cetuximab.

"The traditional approach against this kind of cancer uses cisplatin chemotherapy along with radiation. I had seen data suggesting that the combination of cisplatin and olaparib might be too toxic on patients' blood counts. So our team explored this alternative approach that we hoped would offer a more targeted treatment in this poor prognosis group," Raben says.

In addition to promising survival results, the trial reinforces earlier work showing that cancer patients who continue to smoke while receiving treatment tend to fare worse than those who quit.

"We didn't cherry pick our patients for this trial. All were heavy smokers, many were heavy drinkers, advanced T-stages, and some continued to smoke during the treatment. People who continued smoking were the ones who did the worst," Raben says.

However, the trial's survival benefit came with additional side effects, some of which appeared relatively late in the course of the trial (demonstrating the importance of long-term follow-up for patients in radiation Phase I studies).

"We did see an increase in skin toxicity, which wasn't unexpected, and we learned that when you combine olaparib with radiation, you need perhaps one tenth the dose that you would when using olaparib alone," Raben says. Most common side effects included dermatitis (39 percent) and mucositis (69 percent). Several patients experienced increased long-term fibrosis and one showed carotid stenosis, though Raben points out that some side effects could be due to the continued influence of smoking, as well.

"The question now is whether we should move this combination into a randomized phase II trial or use what we've learned to design new combinations," Raben says. For example, "There is tremendous enthusiasm in the oncology community to combine DNA damage repair inhibitors like olaparib with immune enabling drugs, and this may reduce overall toxicity further when combined with or used after radiation," he says.

Or, Raben suggests that targeted therapies and immunotherapies could be used earlier in the course of treatment, pointing to a forthcoming clinical trial by collaborator Sana Karam, MD, Ph.D., that will test the ability of [radiation](#) and immunotherapy to shrink head and neck cancer tumors before surgery.

"We see this first trial like nurturing a small plant. Now that it's started to grow, its new branches are like new ideas," Raben says. "This trial lays the foundation for testing combinations of targeted treatments against head and [neck cancer](#) in [heavy smokers](#). Hopefully, this trial can also serve as a template for Phase I drug development platforms across disease sites at CU. With our colleagues in the Developmental Therapeutics program, we see this trial laying the groundwork for the development of a novel, self-sustaining Phase I Radiation-Developmental Therapeutics program. Eventually, we hope one of these 'branches' of research will lead to a new paradigm for this population that desperately needs it."

More information: Sana D. Karam et al, Final Report of a Phase I Trial of Olaparib with Cetuximab and Radiation for Heavy Smoker Patients with Locally Advanced Head and Neck Cancer., *Clinical Cancer Research* (2018). [DOI: 10.1158/1078-0432.CCR-18-0467](https://doi.org/10.1158/1078-0432.CCR-18-0467)

Provided by CU Anschutz Medical Campus

Citation: Clinical trial suggests new direction for heavy-smoking head and neck cancer patients (2018, August 14) retrieved 3 May 2024 from <https://medicalxpress.com/news/2018-08-clinical-trial-heavy-smoking-neck-cancer.html>

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