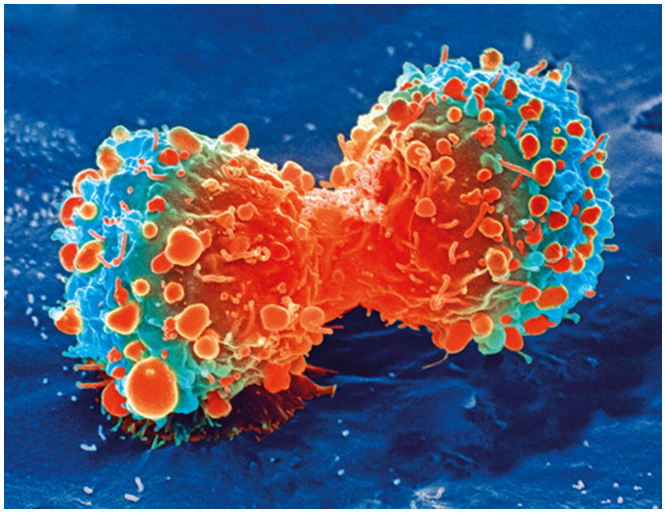
New immunotherapy combination tolerable, effective in patients with advanced kidney cancer

11 February 2018



Cancer cell during cell division. Credit: National Institutes of Health

Combining an anti-angiogenesis agent, which blocks blood vessel formation, with an immunotherapy agent, was found to have promising anti-tumor activity and no unexpected side effects in an early-phase clinical trial in patients with advanced kidney cancer who had not been previously treated, according to a researcher at the Georgetown Lombardi Comprehensive Cancer Center who led this study.

The full findings of the study to date involving the combination of axitinib (Inlyta) and pembrolizumab (Keytruda) will be presented February 10 as part of the ASCO Genitourinary Cancers Symposium in San Francisco, with context and additional information about the primary endpoint to be published simultaneously in The Lancet Oncology.

Axitinib inhibits angiogenesis, the process of blood vessels forming to feed a tumor. Inlyta was approved by the U.S. Food and Drug Administration in 2012 for the treatment of patients with advanced kidney cancer after one prior systemic therapy has failed, and has been shown to be selective in how it works, resulting in a strong effectiveness to toxicity ratio.

The immunotherapy agent, pembrolizumab, is an immune checkpoint inhibitor that blocks a self-defense mechanism used by cancer cells to evade attack and destruction by the body's immune cells. It is FDA-approved for the treatment of patients with several cancer types including melanoma, lung, bladder and head and neck cancers, but has only had limited study in patients with kidney cancer.

Earlier attempts to develop combinations of anti-angiogenesis agents and checkpoint-inhibitor-based immunotherapies to treat patients with advanced kidney cancer resulted in unacceptably high levels of toxicity and thus the combinations were not pursued further. In contrast, the axitinib-pembrolizumab combination was sufficiently tolerable to enable the agents to be given at their FDA-approved single-agent dose levels.

"Our results are unprecedented. The combination doubled the efficacy of the drugs when used alone and the treatment was found to be tolerable," says Michael B. Atkins, MD, deputy director, Georgetown Lombardi Comprehensive Cancer Center and principal investigator for the study. "Specifically, over 90 percent of patients exhibited tumor shrinkage and the disease was kept under control for a median of over 20 months."

The investigators started their phase I clinical trial of this combination in 2014 and enrolled 52 advanced renal cell carcinoma (the most common form of kidney cancer) patients who had not previously been treated for the disease. Their goal

was to find out what dose of the drug could be tolerated by a subset of 11 patients during the first 6 weeks of the trial, then gauge the effectiveness of the therapy in all 52 patients. All enrollees received an intravenous infusion of pembrolizumab at the start of the trial and then every three weeks thereafter. Patients also took axitinib twice daily until they could no longer tolerate the therapy or until no benefit was seen. The researchers looked at tumor size at trial enrollment, then 12 weeks later and every 6 weeks thereafter.

In the 11-patient subgroup, three of the patients were not able to tolerate axitinib and received less than 75 percent of the planned dose due to toxicities, while eight patients experienced manageable side effects, thus establishing this dose level and the recommended dose level for further investigation in a group of 41 additional patients. Significantly, patients had fewer liver abnormalities and less fatigue than those treated with other similar combination therapies, Atkins said. Also, for this new combination therapy, tumor shrinkage or stabilization was better than that seen in patients taking just one of the two drugs alone.

Seventy-three percent of patients experienced significant tumor shrinkage in response to the combination therapy and the median time in which there was no disease progression was 20.3 months. Overall survival results are still incomplete as 88 percent of the patients were still alive at a minimum 18 months after starting therapy. By March 2017, 25 patients were still being treated, with 22 receiving the drug combination and three receiving pembrolizumab only.

"A randomized phase III trial comparing our drug combination to the FDA-approved anti-angiogenesis agent sunitinib is underway and it should tell us if this drug combination is better than the previous standard-of-care regimen," says Atkins. "We think this combination could present a major advance in the treatment of this disease as well as help define effective combinations of similar drugs for other cancers."

More information: Atkins MB, Plimack ER, Puzanov I, Fishman MN, McDermott DF, Cho DC, Vaishampayan U, George S, Olencki TE, Tarazi JC, Rosbrook B, Fernandez KC, Lechuga M, and Choueiri TK. Axitinib in combination with pembrolizumab in patients with advanced renal cell cancer: a non-randomised, open-label, dose-finding, and dose-expansion phase 1b trial. *The Lancet Oncology*. Feb. 10, 2018.

Provided by Georgetown University Medical Center