Do Combination Therapies Hold Hope for Prostate Cancer Patients?

A UCSF trial tests precision radiation with immunotherapy as new treatment for advanced cases of metastatic prostate cancer.

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Cancer immunotherapy drugs have demonstrated limited effectiveness in treating prostate cancer. By contrast, radioligand therapy — a type of precision radiation treatment that uses a targeting compound to damage or destroy prostate cancer cells — has shown improved survival rates in metastatic castration resistant prostate cancer (mCRPC).

In a study published October 31, 2023 in The Lancet Oncology, University of California, San Francisco researchers conducted a phase 1 clinical trial to determine whether a single priming dose of radioligand therapy 177Lu-PSMA-617 [also known as the brand name Pluvicto] combined with pembrolizumab immunotherapy [Keytruda] — an immunotherapy drug, or immune checkpoint inhibitor — would have a beneficial effect in treating patients with mCPRC. Results from the trial demonstrated measurable anti-tumor activity with minimal toxicity in patients with mCRPC.

“This phase 1 trial represents the first clinical study to our knowledge to evaluate a single priming dose of targeted radioligand therapy coupled with immune checkpoint inhibition in patients with metastatic prostate cancer,” said study first author Rahul Aggarwal, MD, a genitourinary medical oncologist and UCSF professor of medicine. “We observed lasting responses in a subset of patients, in whom there was an increase in circulating T cells and decreased activity of immunosuppressive cells following the priming dose of 177Lu-PSMA-617.”

The study included patients with mCRPC and prior treatment with one or more androgen signaling inhibitors, medications that reduce the production of the male sex hormone androgen that contributes to the cancer. A total of 43 male patients were enrolled between August 2019 and July 2022, with a median follow-up period of 16.5 months. Patients received a priming dose of 177Lu-PSMA-617 followed by maintenance pembrolizumab (a sustained dose) administered intravenously every 3 weeks.

Targeted Therapy Enhances Effectiveness

The researchers found significant anti-tumor activity with 56% of participants having a positive response, and a subset of those experiencing durable, or long-term, beneficial responses. The combination therapy showed comparatively low toxicity levels, was not damaging to patients' blood, and had a manageable rate of immune-related adverse events. Within the study cohort, 5% of patients had a complete response to the therapy, 47% had a confirmed partial response, 28% of patients had stable disease and 21% had progressive disease.

"Radiation therapy is an established treatment, but we are still learning how best to combine immunotherapy and radiation therapy," said co-senior author, Lawrence Fong, MD, leader of UCSF's Cancer Immunotherapy Program and the Efim Guzik Distinguished Professor in Cancer Biology. "Our study shows using just a single dose of radioligand therapy, rather than the usual six planned doses, can be combined with immunotherapy and have durable responses."

"Targeted radioligand therapy can enhance the effectiveness of immune checkpoint inhibition by improving priming of an immune response or by resetting the immunosuppressive tumor microenvironment to enhance anti-tumor response," said co-senior author Thomas Hope, MD, vice chair of the UCSF department of radiology. "We thought that if 177Lu-PSMA-617 induced anti-tumor immunity, the immune effector cells recruited to the sites of metastasis would increase with repeated doses given on a fixed schedule."

The researchers acknowledge the limitation of the trial's non-randomized design which does not evaluate the individual contribution of pembrolizumab and 177Lu-PSMA-617. The research team is planning a phase 2 study combining maintenance pembrolizumab with repeated doses of 177Lu-PSMA-617 delivered at variable intervals dependent on the anti-tumor response.

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