Bacterial therapy tolerable, shows early promise in patients with advanced solid tumors

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A phase I clinical trial investigating the use of bacterial Clostridium novyi-NT spores as an injectable monotherapy had manageable toxicities and showed early clinical efficacy in patients with treatment-refractory solid tumor malignancies, according to data presented at the Fourth CRI-CIMT-EATI-AACR International Cancer Immunotherapy Conference: Translating Science into Survival, held Sept. 30-Oct. 3.

"Even after a single injection of this bacterial therapy, we see biological and, in some patients, clinically meaningful activity," said Filip Janku, MD, Ph.D., associate professor at the Department of Investigational Cancer Therapeutics (Phase I Clinical Trial Program), The University of Texas MD Anderson Cancer Center, Houston. "This strategy is feasible, has manageable adverse effects, and could be clinically meaningful in patients with few therapeutic options."

While prior anticancer therapies have utilized bacteria, these treatments can cause infection and severe side effects, explained Janku. C. novyi-NT is an attenuated bacterium that requires a hypoxic environment, a feature of cancerous lesions, to survive and proliferate and therefore does not affect healthy cells, he noted. "By exploiting the inherent differences between healthy and cancerous tissue, C. novyi-NT represents a very precise anticancer therapeutic that can specifically attack a patient's cancer," Janku said.

Janku and colleagues evaluated the intratumoral injection of C. novyi-NT spores in an open-label, first-in-human study. Between November 2013 and April 2017, the researchers enrolled 24 patients with treatment-refractory solid tumors, with 15 patients having sarcoma, seven patients having diverse carcinoma, and two patients having melanoma.

Tumors were injected with a single dose of C. novyi-NT ranging from 10,000 to 3 million spores. Two patients treated with 3 million spores displayed dose-limiting toxicities of grade 4 sepsis and/or grade 4 gas gangrene; the maximum tolerated dose was therefore determined to be 1 million spores.

Of the 22 evaluable patients, 21 had stable disease as measured by RECIST for the injected lesion, with tumor shrinkage of greater than 10 percent observed in 23 percent of patients. When both injected and uninjected lesions were included, the stable disease rate was 86 percent.

Janku noted that RECIST criteria may not accurately capture the results of this trial. "When we inject the tumor, the cells within it die and become necrotic while the remaining tissue becomes inflamed, making the lesion larger in size than the original tumor. Because of this, evaluation via RECIST does not accurately reflect the reduction in tumor burden in these patients."

Janku and colleagues also evaluated the germination of the bacterial spores through clinical and radiological methods. Of the 24 patients enrolled in the trial, tumors from 46 percent displayed spore germination and resultant tumor cell lysis.

"Despite the absence of clinical signs of germination in some patients, we saw improved tumor-specific immune responses through the increased secretion of T-cell cytokines and increased presence of tumor infiltrating lymphocytes in injected tumors," noted Janku. "From these preliminary results, it appears that C. novyi-NT is able to activate the immune response besides causing tumor destruction."

Because C. novyi-NT elicits an innate immune response, Janku believes that this therapy will be synergistic with checkpoint inhibition. The results from this study have led to the initiation of a phase I clinical trial investigating the combination of C. novyi-NT with pembrolizumab (Keytruda).

"We were extremely encouraged by the results of this trial, especially in patients with advanced sarcomas, where immunotherapy hasn't proven very efficacious," Janku said. "This bacteriolytic strategy has the potential to be clinically meaningful, especially in combination with checkpoint inhibitors, for patients with advanced solid tumors."

Limitations of this study include a short follow-up time for some patients, as many entered into other clinical trials if they became available.

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