Combinatorial therapy shows early promise in patients with relapsed small cell lung cancer

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The PARP inhibitor olaparib (Lynparza) in combination with the chemotherapeutic agent temozolomide (Temodar) showed clinical

efficacy in patients with relapsed small cell lung cancer (SCLC), according to results from a phase I/II clinical trial published in *Cancer Discovery*, a journal of the American Association for Cancer Research.

"Small cell lung cancer, which accounts for about 15 percent of all lung cancers, historically has very poor outcomes, and novel treatment strategies are needed for this aggressive cancer type," said Anna Farago, MD, Ph.D., assistant professor of medicine at Harvard Medical School and Massachusetts General Hospital Cancer Center in Boston. "This combinatorial therapy showed encouraging results in patients with relapsed SCLC, representing a new potential therapeutic strategy for these patients who typically have few effective treatment options."

The use of PARP inhibitors has shown limited clinical efficacy in preclinical SCLC models and early phase trials, noted Farago; however, the addition of DNA-damaging agents, such as alkylating agents like temozolomide, may enhance the activity of PARP inhibitors, she said.

This single-arm trial enrolled 50 patients with previously treated SCLC between October 2015 and April 2018; the number of prior lines of therapy ranged from one to seven, with a median of two prior treatments. Thirteen patients were enrolled in the phase I dose-escalation study, with the primary objective of identifying the recommended phase II dose (RP2D). Thirty-seven patients were enrolled in the phase II dose-expansion portion at the RP2D, with the primary objective of evaluating efficacy.

Patients took oral olaparib and temozolomide on days one through seven on a 21-day cycle; the cycle was repeated until disease progression or unacceptable toxicity. Four dose levels were evaluated in the phase I portion, and the RP2D was determined to be 200mg of olaparib twice daily with 75mg/m^2 of temozolomide once daily.

The overall response rate (ORR) among the 48 evaluable patients treated in both portions of the study was 41.7 percent (20 partial responses, no complete responses). Among all 50 patients enrolled in the study, the median progression-free survival and median overall survival were 4.2 months and 8.5 months, respectively. Among evaluable patients treated at the RP2D (39 patients), the ORR was 41.0 percent.

Across both arms of the study, the most common treatment-related adverse events (AEs) were thrombocytopenia (68 percent of patients), anemia (68 percent of patients), and neutropenia (54 percent of patients). Two grade 5 AEs occurred in the phase II portion of the study which were possibly attributable to the study drugs (one due to pneumonia and one due to neutropenic sepsis).

"These two adverse events illustrate that we must inform patients of possible toxicities and diligently monitor blood counts throughout treatment," noted Farago. "While our protocol did not initially offer growth factor support, which is often used in chemotherapy regimens to support neutrophil counts, the protocol was subsequently amended to allow the use of growth factor support after day seven in the treatment cycle."

To identify molecular signatures that may be predictive of response to the olaparib-temozolomide combination, the researchers conducted a co-clinical trial in 32 patient-derived xenograft (PDX) models derived from 22 patients. The researchers determined that a specific molecular signature of four inflammatory response genes (CEACAM1, TNFSF10, TGIF1, and OAS1) could distinguish sensitive from resistant models in both discovery and validation cohorts. Additionally, low basal expression of these genes was associated with resistance to both the investigational combination and to platinum etoposide, the standard first-line chemotherapy for patients with SCLC.

"While biomarkers for drug response have been identified for several cancers, we don't have any good biomarkers of response for small cell lung cancer treatments," said Benjamin Drapkin, MD, Ph.D., oncologist at Massachusetts General Hospital Cancer Center. "Our co-clinical trial in animal models was an important first step in the identification of a potential prognostic signature of response to both the standard first-line chemotherapy and for our investigational combination."

"This combination showed significant clinical activity in patients with relapsed small cell lung cancer, and warrants investigation in a randomized study comparing olaparib plus temozolomide with the standard-of-care option," noted Farago.

Due to the single-arm nature of the trial, these results cannot be directly compared with other therapeutic options in this setting, Farago explained.

More information: Anna F. Farago et al. Combination Olaparib and Temozolomide in Relapsed Small Cell Lung Cancer, *Cancer Discovery* (2019). DOI: 10.1158/2159-8290.CD-19-0582

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