Drug combination shows meaningful responses for malignant peritoneal mesothelioma patients

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A phase II study led by researchers from The University of Texas MD Anderson Cancer Center found that treatment with atezolizumab and

bevacizumab was well-tolerated and resulted in a 40% objective response rate in patients with advanced malignant peritoneal mesothelioma, a rare cancer in the lining of the abdomen. Responses occurred in patients regardless of PD-L1 expression status and tumor mutation burden.

Trial results indicated that the combination was safe and effective in patients with disease progression or intolerance to previous chemotherapy treatment. The study, led by Kanwal Raghav, M.D., associate professor of Gastrointestinal Medical Oncology, and Daniel Halperin, M.D., assistant professor of Gastrointestinal Medical Oncology, was published today in *Cancer Discovery*.

Malignant peritoneal mesothelioma (MPeM) is known as a rare but aggressive disease with historically poor survival and limited treatment options. Because symptoms most often go unnoticed, peritoneal cancer is usually diagnosed at a late stage. If left untreated, life expectancy is often less than a year.

"There is a grave unmet need for patients with peritoneal mesothelioma," Raghav said. "This study establishes a much-needed treatment option and represents an effort to encourage research for this rare disease."

One of the first trials for MPeM patients

Researchers estimate that 300-500 Americans are diagnosed with MPeM each year. MPeM usually follows the same treatment as pleural mesothelioma, a cancer of the lung lining, although there are significant differences between the diseases. MPeM is far rarer, understudied, has a weaker association with asbestos exposure, affects women more frequently, occurs at a younger age and is diagnosed more often at an advanced stage.

Treatment strategies are varied, but usually include optimal cytoreductive surgery, hypothermic intraoperative peritoneal perfusion with chemotherapy (HIPEC) or early postoperative intraperitoneal chemotherapy (EPIC). Patients with MPeM usually are treated following the recommendations for malignant pleural mesothelioma and most studies on chemotherapy drugs have been done for pleural mesothelioma , often excluding MPeM patients.

The National Comprehensive Cancer Network (NCCN) recommends first-line platinum chemotherapy for both mesotheliomas, but after disease progression there is no established treatment strategy or any Food and Drug Administration-approved treatments for advanced MPeM.

This single-center study is a multicohort basket trial for evaluation of atezolizumab and bevacizumab in a variety of advanced cancers. Atezolizumab is a type of immunotherapy drug called an immune checkpoint inhibitor that targets PD-L1, while bevacizumab is a targeted therapy that slows the growth of new blood vessels by inhibiting vascular endothelial growth factor (VEGF). This publication reports data for the 20 patients in the MPeM cohort. The median age was 63 years, 60% of participants were women and 75% self-reported that they had not been exposed to asbestos. Trial participants were 80% white, 10% Hispanic, 5% Black and 5% other.

Prior to enrolling in this clinical trial, patients who received standard of care chemotherapy progressed to next treatment at 8.3 months compared to 17.6 months with atezolizumab and bevacizumab on the study. The median response duration was 12.8 months.

Progression-free and overall survival at one year were 61% and 85%, respectively. The treatment was well-tolerated, with the most common events being hypertension and anemia.

"Patients treated on this regimen surpassed outcomes expected with conventional therapies," Raghav said. "This data shows that this is a reasonable treatment option and reiterates the importance of clinical trials for rare cancers to extend patient survival."

Biomarker analysis

Integration of biopsies before and during treatment established the practicability and the value of a translationally motivated approach in rare cancers. Using the biopsies, the researchers demonstrated that the clinical activity seen with this treatment combination did not correlate with clinically established biomarkers of response to immune checkpoint inhibition in other tumors.

The biomarker analysis determined that epithelial-mesenchymal transition (EMT) gene expression, which is a cancer state associated with a more aggressive biology, correlated with aggressive disease, treatment resistance and poorer response rates.

To define a tumor environment predictive of response to this drug treatment, researchers examined pre-treatment immune cell subsets using 15 available patient samples. They found that VEGF inhibition improves the effectiveness of immune checkpoint inhibitors by adapting the immunosuppressive tumor environment.

"I am very encouraged by the responses to this treatment, and I am hopeful that with additional research this will provide a better treatment option for these patients," Raghav said. "I am thankful for the patients who are willing to participate in clinical trials and help further our knowledge of rare cancers."

Additional trials with larger numbers of patients are needed to validate these study results, determine if this drug combination could be given as

frontline treatment or improve surgical outcomes for these patients.

More information: Kanwal Raghav et al, Efficacy, Safety and Biomarker Analysis of Combined PD-L1 (Atezolizumab) and VEGF (Bevacizumab) Blockade in Advanced Malignant Peritoneal Mesothelioma, *Cancer Discovery* (2021). DOI: 10.1158/2159-8290.CD-21-0331

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