Two targeted therapies act against Ewing's sarcoma tumors

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A pair of targeted therapies shrank tumors in some patients with treatment-resistant Ewing's sarcoma or desmoplastic small-round-cell tumors, according to research led by investigators from The University of Texas MD Anderson Cancer Center reported at the AACR Annual Meeting 2012.

Five of 17 Ewing's sarcoma patients responded to the combination, with two achieving complete responses, one for 27 weeks. The researchers noted that the ability to manage patients' treatment-related side effects is vital to maintaining the therapy and slowing disease progression.

The study was published simultaneously in Clinical Cancer Research, a journal of the American Association for Cancer Research.

Ewing's sarcoma primarily affects the bones and occurs most often in teenagers and young adults and relapse is common, said lead researcher Aung Naing, M.D., assistant professor in MD Anderson's Department of Investigational Cancer Therapeutics.

Researchers used a combination of cixutumumab, a human IgG1 monoclonal antibody that targets insulin growth factor receptor 1 (IGF-1R), and temsirolimus, an agent that inhibits mTOR, or "mammalian target of rapamycin". The two drugs address molecular pathways that cause cell proliferation and survival, abnormal blood vessel growth and resistance to chemotherapy and radiotherapy.

Encouraging Responses in Treatment-Resistant Patients

Twenty patients were enrolled in the phase I clinical trial - 17 with Ewing's sarcoma and three with desmoplastic small-round cell tumors (DSRCT). The patients were treated with cixutumumab (6 mg/kg i.v. each week) and temsirolimus (25 to 37.5 mg i.v. each week) in 4-week cycles. Median follow-up was 8.9 months.

"Seven of the 20 patients responded and have had stable disease for more than five months," Naing said. "Five of these responders have Ewing's sarcoma and have had tumor reductions of more than 20 percent. Treatment responses have lasted 8 to 27 months."

Naing added that these patients had undergone a median of six previous treatments. "They had been heavily, heavily pre-treated and are quite resistant to most other treatments," Naing said. "So we are encouraged that 5 of 17 patients with Ewing's sarcoma-about 29 percent-responded to the treatment, with two achieving complete responses."

The investigators noted that when the two drugs had been used as single agents, treatment results were mixed. They theorized that combining the drugs would help stave off onset of drug resistance, a common occurrence and major obstacle in cancer treatment.

"This trial provides preliminary data indicating that combining two targeted agents can result in tumor regression and even complete remission in heavily pretreated patients with metastatic Ewing's sarcoma, including those whose tumors had progressed on an IGFR inhibitor alone," said study senior author Razelle Kurzrock, M.D., professor and chair of the Department of Investigational Cancer Therapeutics. "By giving combinations of drugs in a scientifically rational way, we may be

able to overcome resistance to single agents and provide benefit to patients with advanced Ewing's sarcoma."

Managing Treatment Toxicities

The most common treatment-related side effects were reduced platelet levels (85 percent), mucositis (80 percent), elevated cholesterol (75 percent), high triglycerides (70 percent), and elevated blood sugar (65 percent).

Naing noted that it is not unusual to see these side effects, which were mostly grade I or grade II in severity. He added that one of the patients developed diabetes, which was eventually managed with insulin and the diabetes medication metformin.

Non-hematologic side effects of the treatment included mucositis, fatigue, rash or itching, elevated AST/ALT, elevated creatinine, diarrhea, anorexia/weight loss, and nausea and vomiting. The ability to manage these and other treatment side effects is critically important, Naing said.

"Our four best responders had grade III mucositis or grade III myelosuppression, such as thrombocytopenia or neutropenia. Typically, a patient who develops these types of grade III toxicities would be removed from the study," Naing said. "But we were able to continue with the treatment after we received approval from the sponsor and notification from our institutional review board. Our patients received the benefits of continued treatment because we were able to manage their toxicities."

Supportive Care Aids Treatment

According to the researchers, the study results suggest patients should receive supportive care that will help them achieve and maintain dose levels high enough to sustain their response.

"If we can manage the toxicity, patients should not be taken off treatment," Naing said. "This is a really important message."

Co-authors Robert Benjamin, M.D., professor and chair of MD Anderson's Department of Sarcoma Medical Oncology, and Joseph Ludwig, M.D., assistant professor in the department, plan further studies in larger numbers of patients with Ewing's sarcoma and DSRCT, as well as additional investigation into underlying resistance mechanisms in individual patients.

Provided by University of Texas M. D. Anderson Cancer Center