Two-drug combo more effective in treating sarcomas, study shows

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Researchers at Moffitt Cancer Center and colleagues at the University of South Florida have found that when given together, a two-drug combination acts synergistically in test animals modeled with sarcoma tumors. They report that the drug combination of MK-1775 and gemcitabine resulted in a 70 percent decrease in the tumor volume when compared to receiving one drug or the other.

Their study was published in the March 8 online edition of *PLOS ONE.*

"Sarcomas are rare tumors affecting both children and adults, but sarcomas account for a greater number of pediatric cancers than adult," said study lead author Soner Altiok, M.D., Ph.D., associate member of the Chemical Biology and Molecular Medicine Program. "Sarcoma response rates to standard chemotherapies have been low, drug toxicity has been high, and improvement in overall survival, especially in metastatic disease, has been negligible. New drugs are needed."

Sarcomas are cancers that result from transformed cells in one of a number of tissues, including bone, cartilage, fat, muscle and vascular tissues. Sarcomas are different from carcinomas, such as breast, colon and lung cancers.

Researchers from Moffitt's Chemical Biology and Molecular Medicine and Sarcoma programs had previously collaborated in testing MK-1775's ability to inhibit Wee1, a protein known to regulate cell size and initiate cell division, an important step in the development of sarcoma. Wee1

plays a role in determining the time at which cell division begins. The researchers found that inhibition of Wee1 by MK-1775 induced cell death in sarcoma tumors.

"Inhibition of the pathways critical to tumor cell survival by molecularly targeted therapy represents an opportunity to reverse the biological basis of tumor formation," Altiok explained.

To further prove that inhibition of Wee1 by MK-1775 leads to cell death in sarcomas cells, the researchers performed additional studies, including studies on sarcomas-related mutations, such as the p53 gene. They also showed that MK-1775 was an active inhibitor of Wee1 regardless of the p53 mutation status of the tumors in the cell lines tested.

"The toxic effect of Wee1 inhibition on sarcoma cells appeared to be independent of p53 mutation status following our testing sarcoma cell lines with different p53 mutations," Altiok said. "All of them were highly sensitive to MK-1775, suggesting that Wee1 inhibition may represent a novel approach in the treatment of sarcomas. But p53 status was not predictive of response to MK-1775 as a single agent."

Because of the success of that previous research, in the new study the Moffitt team investigated the benefits of MK-1775 alone compared to MK-1775 in combination with gemcitabine, a standard chemotherapy drug. They tested the combination in a number of sarcoma cell lines derived from patient tissues and then in animals modeled with osteosarcoma (bone sarcoma).

"The combination of MK-1775 and gemcitabine demonstrated a synergistic effect in sarcoma cells," explained Altiok. "MK-1775 alone caused tumor cell damage, but when used in combination with gemcitabine, there was increased cell death."

When the research team tested the combination in laboratory animals, they found that gemcitabine alone inhibited 40 percent of tumor growth. MK-1775 alone inhibited 50 percent of tumor growth. However, MK-1775 and gemcitabine together inhibited 70 percent of tumor cell growth.

"Our data demonstrated that MK-1775 alone and in combination with gemcitabine induces significant cell death in high-grade osteosarcoma cells," concluded the authors. "This finding lays an important foundation for future clinical trials with MK-1775, which is a well-tolerated, readily available targeted drug."

More information: www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0057523

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