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More chemo drugs don't improve treatment of rare bone cancer

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Osteosarcoma patients with tumors that haven't responded well to the standard chemotherapy regimen have unimproved outcomes and more side effects when given two additional drugs, a large international trial has found.

Adding two chemotherapy drugs to the standard treatment for a rare bone cancer did not improve patients' outcomes and increased toxic side effects, a study of more than 600 patients in 17 countries has found.

The study, which was published Aug. 23 in *The Lancet Oncology*, provides the first head-to-head comparison of two chemotherapy regimens that have been widely used to treat osteosarcoma, a malignant bone tumor. The disease affects about 600 U.S. patients per year, mostly teenagers. Current treatments enable only 65 to 70 percent of patients to live three years past diagnosis without relapse or second cancers, prompting researchers to look for better therapies. Previous small, non-randomized studies suggested that more aggressive chemotherapy with extra drugs might aid some patients, but the new data indicated no benefit from this approach.

"This trial matters because, in the past, we were treating a lot of patients with these drugs without realizing that they weren't helping," said the study's lead author, Neyssa Marina, MD, professor of pediatrics at the Stanford University School of Medicine.

The rarity of osteosarcoma meant that a large, international collaboration

was needed to gather enough patients for a rigorous comparison of the two drug regimens. Doctors at Lucile Packard Children's Hospital Stanford, where Marina is a pediatric oncologist, treat about five to six cases per year, and other large cancer centers have similar numbers of patients.

Most osteosarcomas occur in growing bone, often in the long leg bones near the knee. Treatment consists of chemotherapy to try to kill the tumor, followed by surgery to remove it and then more chemotherapy to get rid of any remaining cancer cells. If the tumor is not at least 90 percent dead when it is surgically removed, the patient has a worse long-term prognosis. Such patients were the focus of the new trial.

Comparing drug combinations

The trial compared two drug combinations. The first, known as MAP, combines methotrexate, doxorubicin and cisplatin. It is the standard osteosarcoma treatment. The second combination, MAPIE, adds the drugs ifosfamide and etoposide. All 618 patients studied had two rounds of MAP chemotherapy followed by surgery, and all were found to have less than 90 percent dead tumor at surgery. After surgery, 310 patients were randomized to receive MAP, while 308 received MAPIE. The trial followed patients for an average of five years and measured "event-free survival," which is the time to a recurrence of the cancer, a second malignancy or death. Treatment side effects were also recorded. MAPIE did not lengthen event-free survival and caused more side effects than MAP.

"The important message from this data is that adding these two drugs does not improve the outcomes of patients who have poor responses to the initial chemotherapy," Marina said. "The drugs shouldn't be added. With them, patients experience more toxicity and more second malignancies." The data is already changing pediatric cancer care, she

added.

The research team believes the next advances in osteosarcoma therapy will require a precision-medicine approach that finds and targets specific cancer-causing gene mutations in different patients, Marina said.

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