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Chemotherapy may influence leukemia relapse: research

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The chemotherapy drugs required to push a common form of adult leukemia into remission may contribute to DNA damage that can lead to a relapse of the disease in some patients, findings of a new study suggest.

The research, by a team of physicians and scientists at Washington University School of Medicine in St. Louis, is published Jan. 11 in the advance online edition of *Nature*.

For patients with acute myeloid leukemia (AML), initial treatment with chemotherapy is essential for putting the cancer into remission. Without it, most patients would die within several months. But even so, about 80 percent of AML patients die within five years when chemotherapy treatment fails to keep the cancer in remission and the disease returns.

Results of the new research provide evidence for a theory that scientists have long held: Chemotherapy contributes to relapse in cancer patients by damaging DNA and generating new mutations that allow tumor cells to evolve and become resistant to treatment.

"The mutations in AML patients who have relapsed are different from those present in the primary tumor, and they are more likely to have a telltale signature of DNA damage," says senior author John F. DiPersio, MD, PhD, the Virginia E. and Sam J. Golman Professor of Medicine and chief of the division of oncology. "This suggests that mutations in the relapse cells are influenced by the chemotherapy drugs the patients receive."

Chemotherapy is known to damage the DNA of both cancer cells and healthy cells. But until now, scientists have had little direct evidence to suggest that chemotherapy itself helps shape the evolution of cancer cells and may contribute to disease recurrence. The researchers suspect this phenomenon is not unique to AML and may occur in other cancers as well.

"Chemotherapy drugs are absolutely necessary to get leukemia patients into remission, but we also pay a price in terms of DNA damage," says co-author Timothy J. Ley, MD, the Lewis T. and Rosalind B. Apple Professor of Oncology. "They may contribute to disease progression and relapse in many different cancers, which is why our long-term goal is to find targeted therapies based on the mutations specific to a patient's cancer, rather than use drugs that further damage DNA."

For the current study, scientists at Washington University's Genome Institute sequenced the genomes – the entire DNA – of cancer cells before and after relapse in eight patients with AML and compared the genetic sequences to healthy cells from the same patients. The data essentially allowed them to map the evolution of cancer cells in each patient.

All the patients received cytarabine and an anthracycline drug to induce remission plus additional chemotherapy in an attempt to keep the cancer from returning. Using technology developed at the Genome Institute, the researchers isolated the DNA segments that contained every mutation in the samples of cancer cells and sequenced those regions nearly 600 times each, far more than the usual 30 times each, which substantially increased the statistical accuracy of the results.

The researchers found that the relapsed cancer cells did not contain a large number of new mutations, as some had predicted. In fact, while the relapsed cells in all the patients had gained some mutations, the

percentage was relatively small compared to the number of mutations in the primary tumor.

The scientists also discovered a type of mutation in the relapsed cells that is associated with DNA damage. The frequency of these alterations, known as transversions, was significantly higher for relapse-specific mutations (46 percent) than for primary-tumor mutations (31 percent), suggesting that the chemotherapy may have contributed to some of these mutations, the researchers report. Transversions are also more commonly found in the tumor cells of lung cancer patients who smoke.

Genome sequencing also revealed two major patterns of evolution of cancer cells linked to AML relapse. All patients had a single founding clone: a cluster of cancer cells – all with the same mutations – that define the leukemia. In some patients, the founding clone gains mutations, enabling it to survive chemotherapy and evolve into the relapse clone. In others, a subclone derived from the founding clone survives chemotherapy, gains mutations and evolves to become the dominant clone at relapse.

"It's the same tumor coming back but with a twist," says co-author Richard K. Wilson, PhD, director of the Genome Institute. "It's always the founding clone or a subclone that comes back with new mutations that give the cells new strategies for surviving attack by whatever drugs are thrown at them. This makes a lot of sense but it's been hard to prove without whole-genome sequencing."

In all cases, the chemotherapy failed to kill the founding clone, an indication that eradicating the founding clone and subclones is the key to achieving a cure.

Sequencing the entire genomes of the cancer cells was essential to the researchers' discoveries. Most of the mutations in the relapse samples

occurred in the regions of the genome that don't include genes and would have been missed if the researchers had sequenced only a portion of the patients' DNA.

"If we only look at the genes, we typically find a total of 10 to 25 mutations in each patient with AML," says lead author and Genome Institute scientist Li Ding, PhD, research assistant professor of genetics. "That's not enough to see significant changes in the mutational patterns of the primary tumor cells versus those in the relapsed cells. Whole-genome sequencing identifies hundreds of mutations in each patient, which provides the resolution and confidence necessary for us to dig deeper to understand how cancer evolves."

DiPersio, who regularly treats patients with AML, says, "Our preconceived notion of the clonal evolution of AML and other cancers has been altered by our study, which suggests that it is much more complicated and dynamic than we initially suspected and can even be impacted by the therapy that is given to treat the disease."

About 13,000 cases of acute myeloid leukemia are diagnosed each year in the United States. It occurs most often among those age 60 or older and becomes more difficult to treat as patients age. According to the American Cancer Society, the five-year survival rate for AML is 21 percent.

More information: Ding L, Ley TJ, Mardis ER, Wilson RK and DiPersio JF et al. Clonal evolution in relapsed acute myeloid leukemia revealed by whole-genome sequencing. *Nature*. Advance online publication Jan. 11, 2012.

Provided by Washington University School of Medicine