Discovery may help prevent chemotherapy-induced anemia

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Cancer chemotherapy can cause peripheral neuropathy—nerve damage often resulting in pain and muscle weakness in the arms and legs. Now, researchers at Albert Einstein College of Medicine of Yeshiva University have discovered that chemo also induces an insidious type of nerve damage inside bone marrow that can cause delays in recovery after bone marrow transplantation. The findings, made in mice and published online today in *Nature Medicine*, suggest that combining chemotherapy with nerve-protecting agents may prevent long-term bone marrow injury that causes anemia and may improve the success of bone marrow transplants.

Constantly regenerating and maturing, the hematopoietic (blood-producing) stem cells in our bone marrow produce billions of red blood cells (RBC) every day. Cancer chemotherapy is notorious for injuring the bone marrow, leading to anemia, or low RBC counts. But just how chemotherapy harms the bone marrow has not been clear.

Anemia can lead to numerous health problems including chronic fatigue, tachycardia (abnormally rapid heartbeat), cognitive impairment, shortness of breath, depression and dizziness. In addition, studies have shown that cancer patients who develop anemia have a 65 percent increased risk of death compared with cancer patients without anemia.

In an earlier study, senior author Paul Frenette, M.D., professor of medicine and of cell biology and director of the Ruth L. and David S. Gottesman Institute for Stem Cell and Regenerative Medicine Research

at Einstein, found that sympathetic nerves within bone marrow direct the movement of hematopoietic stem cells. (The body's sympathetic nervous system helps in controlling most internal organs—increasing heart rate and dilating the pupils of the eye, for example.)

"Since many chemotherapies used in cancer treatment are neurotoxic, we wondered whether they might also damage sympathetic nerves in bone marrow itself, impairing the ability of hematopoietic cells to regenerate and to manufacture RBCs," said Dr. Frenette. "This possibility hadn't been examined before."

Dr. Frenette and his colleagues treated mice with seven cycles of cisplatin, a common chemotherapy drug with known neurotoxic effects. The cisplatin caused peripheral neuropathy problems similar to those seen in cancer patients. The mice were then given fresh bone marrow transplants to see how well their marrow would regenerate. Despite receiving fresh stem cells, the cisplatin-treated mice had delayed recovery of blood counts compared to controls—suggesting that the prior cisplatin treatments had affected the bone marrow and prevented hematopoietic stem cells from regenerating. By contrast, mice treated with carboplatin—a non-neurotoxic chemotherapy—recovered their ability to produce blood after bone marrow transplantation.

To confirm that healthy sympathetic nerves in the bone marrow are needed to regenerate hematopoietic stem cells and produce RBCs, the researchers selectively damaged sympathetic nerves in bone marrow using chemicals or genetic engineering. In both cases, the mice with the damaged sympathetic nerves were less able than control mice to recover after bone marrow transplant.

The researchers found that injury to these nerves could be reduced by giving mice nerve-protecting agents along with chemotherapy. Mice treated with seven cycles of cisplatin along with 4-methylcatechol (an

experimental drug that reportedly protects sympathetic nerves) showed improved response to bone marrow transplantation, compared to controls.

Dr. Frenette and his colleagues now plan to look for compounds that can protect sympathetic nerves in the bone marrow without reducing the effectiveness of cancer chemotherapies.

More information: Chemotherapy-induced bone marrow nerve injury impairs hematopoietic regeneration, DOI: 10.1038/nm.3155

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