Direct-to-brain chemo better than systemic drugs when immunotherapy is to follow

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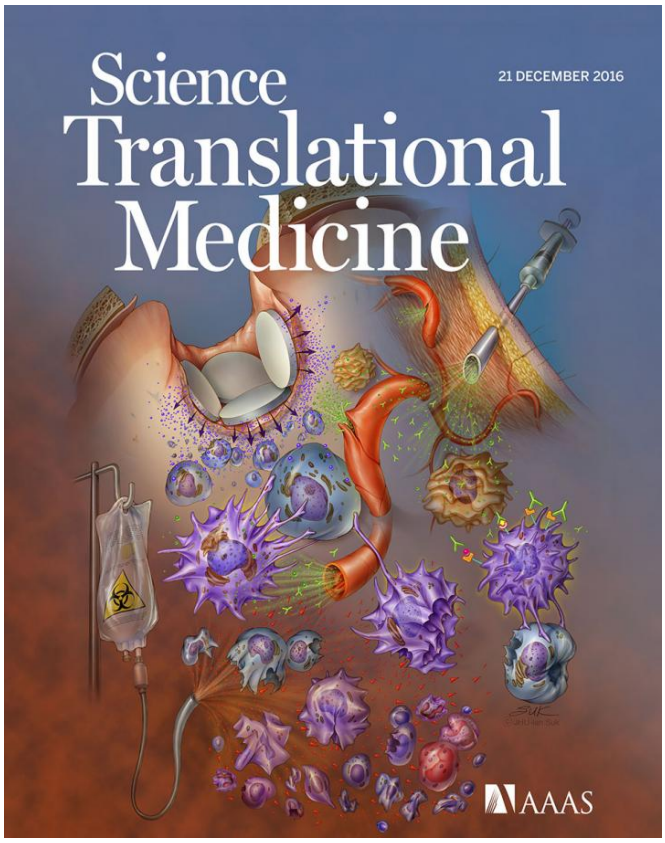

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In experiments on mice with a form of aggressive brain cancer, Johns Hopkins researchers have shown that localized chemotherapy delivered directly to the brain rather than given systemically may be the best way to keep the immune system intact and strong when immunotherapy is also part of the treatment.

The researchers say their study results, reported Dec. 21 in *Science Translational Medicine*, could directly affect the design of immunotherapy clinical trials and treatment strategies for people with a deadly form of brain cancer called glioblastoma.

"We understand that our research was done in a mouse model and not in humans, but our evidence is strong that systemic chemotherapy alters the immune system in a way that it never fully recovers," says Michael Lim, M.D., associate professor of neurosurgery and director of brain tumor immunotherapy at the Johns Hopkins University School of Medicine, and member of the Johns Hopkins Kimmel Cancer Center. "With aggressive cancers like glioblastoma, it is important that we don't handicap the defenses we may need to add alternative treatments, such as immunotherapy, to chemotherapy," he adds.

Lim's laboratory in neurosurgery and a team from the Bloomberg~Kimmel Institute for Cancer Immunotherapy led by Drew Pardoll, M.D., Ph.D., performed their studies in a mouse with glioblastoma. In people, glioblastoma is a particularly aggressive form of cancer, with a typical survival time of just over a year after diagnosis. Current treatments include surgical removal of the visible tumor, radiation and chemotherapy. Because the disease is so lethal, even after aggressive standard treatment, neurosurgeons like Lim are looking to add newer immunotherapies that use the body's own immune system cells to fight the tumor.

However, one challenge to immunotherapy, Lim says, has been the potential toxic effects of systemic therapies that could damage or interfere with the immune system and weaken the chances for success of immunotherapy approaches. With clinical trials being designed to integrate standard of care with immunotherapy, Lim and his team sought to create a way to accurately assess the impact of localized versus systemic chemotherapy on the immune system's ability to stay healthy, and to see which kind of chemotherapy would actually improve survival time in the test mice.

To determine if one method of chemotherapy delivery was better over another when combined

with immunotherapy, the researchers first gave a group of mice with glioblastoma clinically relevant doses the immunotherapy drug anti-PD-1 (200 milligrams per kilogram) and then treated the mice with chemotherapy either throughout the whole body or directly to the brain over two weeks.

For the whole-body, or systemic, chemotherapy, the mice were injected in their bellies with 30 milligrams per kilogram of the chemotherapy drug carmustine—the same drug used against glioblastoma in people—three times a week. Each treatment group contained 15 mice. For the local chemotherapy, the researchers directly implanted a wafer covered in molecules that bound carmustine, allowing sustained release of the drug over a week, into mice with established brain tumors.

The researchers first took blood samples from the rodents' lymph nodes, brain, bone marrow and blood a couple of days after the end of the chemotherapy treatments, almost two weeks later and at the four-month mark. They focused on counting the number of white blood cells called lymphocytes (T cells) as a way to measure immune system integrity. The mice given systemic chemotherapy had much lower levels of lymphocytes than the mice given the local, long-lasting chemotherapy. For example, two weeks after treatment, mice with systemic chemotherapy had only about a third of the lymphocytes in their circulating blood as mice given the local chemotherapy. The researchers say their findings align with what is observed clinically in patients who received systemic chemotherapy. Lim says the suppression is suggested that the lymphocyte depletion caused by systemic chemotherapy is likely counterproductive to producing an effective antitumor immune response.

Next, the team wanted to see if local versus systemic chemotherapy in conjunction with immunotherapy affected survival in the mice with glioblastoma. The scientists found that when they gave the mice chemotherapy locally, it acted together with the immunotherapy drug to improve survival to about 80 percent after 100 days when compared to mice receiving immunotherapy alone, local chemotherapy alone, or combined systemic chemotherapy and immunotherapy, with a survival rate of about 50 percent after 100 days. Then, they followed up these experiments by assessing the immune system's memory. They gave mice local chemotherapy or systemic chemotherapy in conjunction with immunotherapy, and then implanted them with more tumors. The mice with the systemic chemotherapy and immunotherapy all died when injected with extra tumors. But the mice with local chemotherapy and immunotherapy survived, essentially immunized against their glioblastoma. The researchers say this suggests that the systemic chemotherapy profoundly weakens the immune system. The researchers showed that the immune system weakening phenomenon isn't specific to carmustine and happens in multiple types of systemic chemotherapy, such as temozolomide.

The researchers also reversed the treatment protocols, giving the chemotherapy before the immunotherapy to see if that worked better and improved survival. They didn't notice a difference in survival time whether the immunotherapy was given before or after the brain-specific chemotherapy.

Only 10 percent of people diagnosed with glioblastoma live more than five years, according to the American Brain Tumor Association. Glioblastoma mostly occurs in people over 45 and in men somewhat more often than in woman. An estimated 15 percent of the 78,000 people diagnosed with brain tumors in the U.S. each year will be diagnosed with glioblastoma.

Currently, a large number of immunotherapy trials are underway for patients with glioblastoma. There are only three immunotherapy drugs that are FDA-approved for treating other types of cancer, and they cost over $100,000 annually.

More information: D. Mathios et al, Anti-PD-1 antitumor immunity is enhanced by local and abrogated by systemic chemotherapy in GBM, *Science Translational Medicine* (2016). DOI: 10.1126/scitranslmed.aag2942

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