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# Fighting brain tumors while protecting the brain

## The stem cell story

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**HOW ARE BRAIN TUMORS TREATED?** There are many types of brain tumors. Some are the result of the spread of cancer from one part of the body (for example, a lung cancer) to the brain. This article focuses on treatment of a different group of tumors that arise from the cells of the brain itself. These are called primary brain tumors. Primary brain tumors are fairly common: about 22,000 people in the United States find out that they have a primary brain tumor each year.

Many of the primary brain tumors arise from cells in the brain called glial cells. Glial cells play an important supportive role to the main brain cells, which are called neurons. Tumors that arise from glial cells are referred to as gliomas. Some gliomas are treated effectively with surgery, some require treatment with radiation therapy, and many are treated with chemotherapy. Chemotherapy may be used alone, but is often used in combination with other treatments.

One major concern about treating primary brain tumors is that the treatments are not perfectly selective. In other words, in trying to kill the tumor cells, some important normal brain cells—innocent bystanders—are injured in the process. This can lead to problems with concentration, thinking, or memory—something that has been informally called “chemo brain.” It is clear that people who suffer learning and memory problems from their tumor treatments have a lower quality of life.

**WHAT ARE NEURAL STEM CELLS AND GLIOMA-LIKE STEM CELLS AND WHY ARE THEY IMPORTANT?** Many years ago it was thought that we were born with a certain number of neurons, and that by adulthood, we were unable to make any new neurons. Much scientific work, especially over the past 2 decades, has made it clear that neural stem cells (NSCs)—those cells that can develop into new neurons—are found in adults. These NSCs appear to be especially important for learning and memory. Injury to NSCs from tumor treatments such as radiation therapy and chemotherapy might explain some of the reason for “chemo brain.” We know that NSCs in rats can be injured by radiation therapy and chemotherapy, but we know less about the effects on human NSCs.

There is a group of similar stem cells called glioma-like stem cells (GSCs). In some ways these

look like NSCs, but they are believed to drive tumor growth. We do not know very much about the effects of chemotherapy on GSCs.

**WHAT DID THE AUTHORS WANT TO FIND OUT?** Dr. Gong and his colleagues<sup>1</sup> wanted to find out more about the effects of older and new chemotherapy drugs on human stem cells. Because this is hard to study in people, they instead studied cell cultures. Cell cultures are basically groups of specific types of cells grown in a dish. They were able to grow both NSCs and GSCs and test the effects of chemotherapy on the cells. They wanted to find out which types of chemotherapy could kill the GSCs (to help stop tumor growth) but not hurt the NSCs (to avoid “chemo brain”). They studied 2 common older forms of chemotherapy: TMZ (temozolomide) and CIS (cisplatin). They also looked at the effects of 2 newer forms of chemotherapy that are being studied: ERL (erlotinib) and BTZ (bortezomib).

After exposing cells to the different forms of chemotherapy, they measured the effects in several ways. They looked at how many cells died. They also looked at how rapidly the remaining cells divided. They looked at whether cells had signs of resistance to chemotherapy.

**WHAT DID THEY FIND?** The important finding was that not all forms of chemotherapy affected NSCs and GSCs in the same way.

1. A commonly used chemotherapy drug (TMZ) was more likely to kill NSCs than GSCs. This means that it appears to affect the normal NSCs more than the tumor-related stem cells (GSCs). Both types of cells showed some signs of resistance to chemotherapy (TMZ), so this did not explain the difference in the effects of TMZ.
2. Another commonly used older chemotherapy drug (CIS) showed similar findings. There were severe effects on the health of normal NSCs, but little to no effect on the tumor stem cells (GSCs). This is exactly the opposite of what we would like to see. There was some evidence that the GSCs had more of one form of drug resistance. This might partly explain the difference in drug effects.

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- Both of the newer chemotherapy drugs being studied (BTZ, ERL) had greater effects in killing the tumor stem cells (GSCs) than normal NSCs. They uncovered some possible mechanisms for why these drugs worked differently from the older drugs.

**WHAT DOES THIS MEAN FOR PATIENTS WITH BRAIN TUMORS?** We know that chemotherapy can affect attention, learning, and memory. These changes can affect quality of life. The current study by Gong and coworkers takes an important step toward trying to understand why this happens and exploring some possible ways these problems could be avoided.

It is important to remember that these studies were done in cell cultures, not in people. It is a big leap to say that the same thing happens in people who receive chemotherapy. There are examples of other studies where the effect in people is different than in cell culture. We still need to know more about how effective the newer drugs studied (BTZ,

ERL) are at treating primary brain tumors. While doing this, we need to pay attention to their effects on learning and memory.

This is an exciting new way to think about how to make chemotherapy safer and more effective, and we all look forward to the next chapter in this story.

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American Academy of Neurology

<http://patients.aan.com>

National Brain Tumor Society

<http://www.brainumor.org>

American Brain Tumor Society

<http://www.abta.org>

National Cancer Institute

<http://www.cancer.gov>

#### REFERENCE

- Gong X, Schwartz PH, Linskey ME, Bota DA. Neural stem/progenitors and glioma stem-like cells have differential sensitivity to chemotherapy. *Neurology* 2011;76: 1126–1134.

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