

AMERICAN BRAIN TUMOR ASSOCIATION

# Chemotherapy



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## ACKNOWLEDGEMENTS

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Founded in 1973, the American Brain Tumor Association (ABTA) was the first national nonprofit organization dedicated solely to brain tumor research. The ABTA has since expanded our mission and now provides comprehensive resources to support the complex needs of brain tumor patients and caregivers, across all ages and tumor types, as well as the critical funding of research in the pursuit of breakthroughs in brain tumor diagnoses, treatments and care.

To learn more, visit **abta.org**.

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# Chemotherapy

## INTRODUCTION

“Chemotherapy” is the use of drugs to treat cancer. Chemotherapy drugs are used to treat both low-grade and high-grade brain tumors.

## ABOUT CHEMOTHERAPY

Almost every cell in the body is capable of duplicating itself into two new cells. Those two cells double into four, the four into eight, and so on. This process of cell division is controlled by signals and switches on the inside and outside of cells. These signals and switches tell the cells to divide or not. Uncontrolled cell divisions form a mass called a tumor.

The goal of chemotherapy is to stop tumor cell growth and proliferation directly by making them unable to duplicate themselves or to artificially start the normal process of cell death called “**apoptosis.**” In normal organs, apoptosis controls the number of cells in our body at any given time and provides signals to the body when new cells are needed.

In the case of cancer, the tumor cells may be resistant to apoptosis or reproduce more rapidly than the number of cells dying, leading to tumor growth.

Chemotherapy drugs are used to stop this growth process, to alter the behavior of tumor cells or to kill the tumor cell directly. **There are two broad categories of chemotherapy drugs: “cytostatic”** drugs, also called targeted or biologic drugs, which prevent cell division; and **“cytotoxic”** drugs, which are intended to lead to cell death.

## HOW CHEMOTHERAPY WORKS

In order for a cell to split itself into two normal cells, through a process called mitosis, the “parent” cell must complete several tasks in a very specific order. This list of tasks is called the cell cycle. It includes jobs such as making the proteins and enzymes needed to fuel the cell’s reproductive process, duplicating the DNA within the cell, and then separating that DNA into sets – one set for each new cell.

Chemotherapy drugs can stop cells from starting or completing the cell cycle by interfering with this reproductive process (cytostatic, targeted or biologic agents) or causing cell death (cytotoxic agents).

## TYPES OF CHEMOTHERAPY

**As noted earlier, chemotherapy drugs can be generally classified as those that prevent cell division or growth (cytostatic drugs) or those that lead to cell death (cytotoxic drugs).** Within those broad categories, chemotherapy drugs are then grouped by the way they work and the effect they have on tumor cells.

## Cytostatic drugs

### Anti-angiogenesis inhibitors

A tumor requires nutrients in order to grow; those nutrients make their way to the tumor via an elaborate system of blood vessels the tumor develops to maintain an adequate food supply. **The growth of these blood vessels around a tumor is “angiogenesis;” interference with their growth is “angiogenesis inhibition.”** Thalidomide, interferon, bevacizumab (Avastin), cilengitide (EMD 121974), cediranib (Recentin) VB-111, and other antiangiogenic drugs are being tested for their potential to stop the growth of a tumor’s blood supply. Additionally, these agents may even straighten tortuous blood vessels to better deliver chemotherapy. Overall, antiangiogenic agents are sometimes combined with chemotherapy drugs in an effort to increase the effectiveness of both.

### PARP inhibitors

There are enzymes found in normal and cancer cells that may actually help cancer cells repair the destruction caused by chemotherapies. PARP, or poly-ADP ribose polymerase, is a protein found in cells, involved in a number of cellular processes such as DNA repair, and genomic stability. Drugs are being developed to inhibit these repair enzymes. PARP inhibitors are examples of this group of drugs, which are being tested in clinical trials in the hope of countering this resistance.

### Growth factor inhibitors

Normal cell growth requires “growth factors” that are signals that tell cells to grow and proliferate. Inappropriate levels of growth

factors, however, may cause the overgrowth of cells and the subsequent development of a brain tumor. Tyrosine kinase inhibitors, such as imatinib mesylate (Gleevec), and drugs that interfere with growth factor receptors, such as gefitinib (Iressa), erlotinib (Tarceva), sorafenib (Nexavar) and cediranib (Recentin), are being studied.

## CYTOTOXIC DRUGS

**Alkylating agents** work by forming a molecular bond in the DNA strands inside tumor cells, which prevents them from successfully replicating. Carboplatin, cisplatin, cyclophosphamide and temozolomide (Temodar) are examples of alkylating agents. *Nitrosoureas* are a subclass of alkylating agents. They stop tumor cells from repairing themselves and thus render them unable to divide. Carmustine (BCNU) and lomustine (CCNU) are nitrosoureas.

**Antimetabolites** stop tumor cells from making the enzymes needed for new cell growth. Methotrexate (MTX) is an example of an antimetabolite.

### Inhibitor of Internal Signal in Nutrient-Sensing

**Signaling cascade** stop the action of enzymes needed for cell growth, and may be able to change the environment around the cell. Rapamycin, for example, is an anti-tumor antibiotic.

**Hormones** may be capable of interfering with tumor growth by blocking the production of certain proteins in the tumor

cells. For example, tamoxifen is a hormone-based drug also used to treat breast cancer. In studying the way the drug works, researchers observed that tamoxifen may be capable of suppressing some of the proteins involved in the growth of malignant brain tumors. It is a protein kinase C inhibitor.

**Mitotic inhibitors** interfere with the production of the proteins needed to create new cells. Etoposide (VP-16), paclitaxel (Taxol) and vincristine are examples of mitotic inhibitors.

**Steroids** are used to decrease swelling around the tumor. While they are not intended to be "cytotoxic" therapy, some researchers do believe steroids have some toxic effect on tumor cells. If true, this effect is probably not enough to kill significant numbers of cells. One exception to this, however, is primary CNS lymphoma, which is, initially, particularly sensitive to steroids. Rather than controlling edema, steroids destroy lymphoma tumor cells, but they typically do not provide long-term control of the tumor.

These treatments work differently than classic chemotherapy that impairs the cell during the process of cellular division.

### **Cell-cycle specific and cell-cycle nonspecific drugs**

Some chemotherapy drugs act during specific parts of the cell cycle; thus, those drugs are called "cell-cycle specific" drugs. Other drugs are effective at any time during the cell-cycle; those are called "non cell-cycle specific" drugs.

Sometimes chemotherapy treatment plans use a combination of cell-cycle specific and cell-cycle non-specific drugs in an attempt to treat a larger number of tumor cells.

#### Cell-cycle specific drugs

- Hormones
- Steroids
- Etoposide (VP-16)
- Hydroxyurea
- Methotrexate (MTX)
- Procarbazine (Mitalane)
- Temozolomide (Temodar)

#### Cell-cycle non-specific drugs

- Bevacizumab (Avastin)
- Cilengitide (EMD121974)
- Cisplatin (CDDP)
- Carmustine (BCNU)
- Lomustine (CCNU)
- Irinotecan (CPT-11)
- Rapamycin
- Vincristine (VCR)

## WHEN CHEMOTHERAPY MAY NOT BE RECOMMENDED

There are reasons why chemotherapy might not be suggested as a treatment for your tumor.

### **Not all brain tumors are sensitive to or respond to chemotherapy**

If it is known that your type of tumor does not respond to chemotherapy or if it becomes resistant to the drug that is being used, other treatments can be recommended. Your tumor may be able to be removed with surgery alone or may be sensitive to radiation therapy. Some tumors respond to treatment with hormones or drugs that control hormone production. Other tumors may be sensitive to some of the new biologic therapies.

**Chemotherapy affects both normal and tumor cells**

Although chemotherapy drugs have a greater effect on rapidly reproducing cells – such as tumor cells – the drugs cannot always tell the difference between normal cells and tumor cells. The “side effects” of chemotherapy are really the effects of the chemotherapy drugs on those normal cells.

**Chemotherapy drugs effect some normal cells to a greater degree than others.** Cells which “turn over” or regenerate rapidly are also the most vulnerable to side effects. These particularly sensitive normal components of your body include the cells which line the mouth and the gastrointestinal tract. For example, some chemotherapy drugs cause mouth sores. Those “sores” are actually the shedding of the normal cells lining the mouth. Diarrhea occurs because the rapidly reproducing cells of the GI tract are also very sensitive to chemotherapy. Good general health prior to starting chemotherapy helps the body heal itself during and after chemotherapy, but this healing takes time.

**Additionally, because of their constant turn over, normal blood cells are susceptible to the effects of chemotherapy.** Therefore, your physician will monitor your blood counts, which includes monitoring white blood cells, which fight infections; platelets, that help clot blood; and red blood cells, which deliver oxygen to your tissues. Your physician will discuss how regularly (s)he will monitor your counts and what will be done if your blood counts drop. (S)he will also discuss the long-term risks to your blood cells even after chemotherapy has stopped.

## HOW CHEMOTHERAPY IS DELIVERED

Scientists have developed different ways of getting chemotherapy drugs to the tumor cells. Some of these methods require the drug to spread through the body, via the bloodstream, to the brain. This is called “systemic delivery.” Other methods focus on placing the drug within or around the tumor. This is called “local delivery.”

### **Systemic delivery**

Some systemic drugs are given by mouth, also called “orally.” Lomustine (CCNU) and temozolomide (Temodar) are examples of systemic drugs. They travel through the body via the blood, are able to cross the blood-brain barrier and into the tumor cells. Both CCNU and Temodar are pills. Some systemic drugs are given by injection. Injection routes may be:

- Into a vein, also called “intravenous” or “IV” delivery (the most common)
- Into an artery, also called “intra arterial” or “IA” delivery
- Into a muscle, also called “intramuscular” or “IM” delivery
- Into the skin, also called “subcutaneous” or “subcut” delivery

### **Local delivery**

Some drugs can be placed closer to the tumor or within the areas of tumor growth. The goals of local delivery are to avoid delivering drugs throughout the body and to increase the concentration of drug at the tumor site.

The variations in local delivery are:

- Into the cavity left by tumor removal, also called “intracavitary” delivery
- Into the surrounding brain tissue, also called “interstitial” delivery
- Into the cerebrospinal fluid, also called “intrathecal” delivery
- Into the tumor by use of gravity or controlled flow, called “convection enhanced delivery”
- Into the tumor, also called “intratumoral” delivery
- Into a ventricle, also called “intraventricular” delivery

## TREATMENT SCHEDULE

The doctor who suggests chemotherapy for your tumor will provide you with a treatment plan, or schedule, of the days the drugs will be given. Your schedule will be specific to the type of drug(s) recommended for your tumor, and it may be a different schedule than other people you meet who are going through chemotherapy.

A chemotherapy treatment plan may also be based on the purpose of the drug. For example, **radiosensitizers** are drugs used to make a tumor more sensitive to radiation therapy, and are therefore used before or during radiation. **Some chemotherapy may be given before radiation (neoadjuvant), during radiation (concurrent) or after completion of radiation (adjuvant). In addition, chemotherapy may be given without radiation as treatment or as a maintenance therapy.**

Your treatment schedule may also be impacted by the way your body responds to the drugs and by side effects you may experience.

**Common side effects associated with cytotoxic chemotherapy** include hair loss, nausea and vomiting, diarrhea or constipation, fatigue, and lowered blood counts.

**Cytostatic chemotherapy often has side effects** that are different than the traditional side effects associated with chemotherapy. For example, rashes on the hands or face, fatigue or sleepiness, hypertension, skin dryness, or bleeding with a normal platelet count may occur. It is important to talk to your health care team if you are receiving a newer drug, to be sure what to expect with your particular treatment.

Blood tests will be done at regular times during your chemotherapy treatment to monitor the impact on blood counts. Chemotherapy particularly affects white blood cells (which fight infection), red blood cells (which carry oxygen around your body) and platelets (which help the blood to clot). It is not unusual for a person's blood count to be lower during treatment, but this does not necessarily alter your treatment schedule. However, if you have any indication of an infection, such as a fever or abnormal bleeding, notify your doctor immediately. Your next chemotherapy treatment might be postponed until your blood count recovers, but this is ultimately for your benefit.

If your blood cell count begins to drop, ask your doctor at what level you should be concerned. If your blood count reaches that level, ask for tips on protecting your health until those counts begin to increase. Some simple precautions can help get you back on the road to wellness.

After your doctor outlines your chemotherapy schedule, talk it over with your family. Planning can help you address the practicalities of being in treatment. Sometimes chemotherapy goes on for a year or more. Arranging a new daily schedule for yourself and/or your family can help make the transition a bit easier. Flexible work schedules, part-time or full-time child care, pre-prepared meals, frequent rest periods, and fewer activities for a couple of days following your treatment can help minimize the impact of the chemotherapy schedule on your life.

### SIDE EFFECTS

The side effects of chemotherapy are specific to the drug, or drugs, being used. When your doctor outlines a treatment plan for you, ask for fact sheets or “drug sheets” about each of the drugs suggested.

Included below are the more commonly used brain tumor drugs and some of their side effects. Your health care team can talk with you about the chances of these effects occurring based on your treatment plan, and how to care for yourself while taking these drugs.

**Bevacizumab (Avastin):** delayed wound healing; high blood pressure; risk of bleeding or stroke; and excessive protein in the urine. Other, less common side effects may include dizziness, shortness of breath and muscle pain. Rare, but serious side effects associated with bevacizumab include holes in the esophagus and gastrointestinal tract; sudden bleeding at the tumor site; kidney damage; a severe increase in blood pressure possibly leading to a stroke; and heart failure.

**Carboplatin:** nausea and vomiting; bleeding; lowered white cell counts; lowered red cell counts; numbness or tingling in the hands and feet; and hair loss.

**Carmustine given intravenously (BCNU, BiCNU):** fatigue; pain at the injection site; nausea and vomiting; lowered white cell count; lowered red cell count; bleeding; hair loss; diarrhea; confusion; breathing problems; lowered blood pressure; and mouth and throat sores. When administered in polymer wafer implants (Gliadel), side effects may include headache; nausea and/or fatigue due to temporary increased swelling in the brain. Less common, more serious side effects include seizures; brain edema (swelling); wound infection; partial paralysis (hemiplegia); and language difficulty (aphasia).

**Cisplatin (Platinol):** hearing changes; nausea and vomiting; kidney damage; lowered white cell count; lowered red cell count; bleeding; numbness or tingling in the hands and feet; foot drop; metallic taste to food; and appetite changes.

**Etoposide (VP-16):** lowered red cell count; bleeding; lowered white cell count; nausea and vomiting; constipation; decreased blood pressure; hair loss; fatigue; mouth and throat sores; and decreased appetite.

**Hydroxyurea (Hydrea):** lowered white cell count; bleeding; lowered red cell count; nausea and vomiting; diarrhea; constipation; rash; itching; fatigue; mouth sores; and decreased appetite.

**Irinotecan (CPT-11 or camptosar):** anxiety; diarrhea; changes in stool and urine color; heartburn; indigestion; nausea and vomiting; redness; numbness or tingling sensations in the hands or feet; dizziness; skin rash; drowsiness; low blood counts; hair loss; and sleeplessness.

**Lomustine (CCNU):** nausea and vomiting; lowered white cell count; bleeding; mouth sores; hair loss; and lowered red cell count.

**Methotrexate (MTX):** mouth sores; lowered white cell count; nausea and vomiting; diarrhea; lowered red cell count; bleeding; fatigue; darkening of the skin; hypersensitivity to sun; liver damage; kidney damage; and decreased appetite.

**Procarbazine (Matulane):** nausea and vomiting; confusion; numbness or tingling in the feet and hands; hair loss; depression; nervousness; sleeplessness; appetite changes; lowered white cell count; bleeding; lowered red cell count; muscle aches; fatigue; alcohol intolerance (severe nausea and vomiting if alcoholic beverages are consumed); reactions to food with high-tyramine content (see your doctor for a list of foods to be avoided); and darkened skin color.

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**Tamoxifen (Nolvadex):** hot flashes; menstrual changes; menopause symptoms; blurred vision; increased fertility (talk with your doctor about this); vaginal discharge; blood clots; temporary memory loss; and increased risk of uterine cancer with long-term use.

**Temozolomide (Temodar):** nausea and vomiting; headache; fatigue; seizures; constipation; diarrhea; weakness; bleeding; lowered white cell count; lowered platelet counts; and anemia.

**Vincristine (Oncovin):** numbness or tingling of the hands and feet; constipation; nausea and vomiting; vision changes; light sensitivity; depression; drowsiness; confusion; hoarseness; mouth sores; fatigue; hair loss; muscle weakness; problems urinating; and jaw pain.

## MANAGEMENT OF SIDE EFFECTS

Your health care team can give you helpful tips and practical information, and can put you in touch with resources to help you feel better through treatment. Included here are just a few samples of the type of information available to you as you move through treatment. These resources can help you better control possible treatment effects and help you feel your best through, and beyond, treatment. Whether you are being treated in a hospital setting, outpatient clinic or at home, your health care team can help.

In addition, the American Brain Tumor Association can help you find wigs, hair accessories, home care services, patient and caregiver support networks and more. The ABTA can help you and your family understand the assistance offered to you through rehabilitative medicine programs, memory retraining, physical and occupational therapy services, and variety of other resources. Call our CareLine at 800-886-ABTA (2282) or reach us by e-mail at [abta cares@abta.org](mailto:abta cares@abta.org).

### **Vomiting**

One of the most feared effects of chemotherapy is vomiting. Remarkable advances have been made in the development of a new generation of drugs called anti-emetics, which control this effect.

Prior to starting treatment, ask your health care team if the drug prescribed for you will cause nausea or vomiting. If so, be sure you are provided with an "anti-emetic plan" specific to the chemotherapy drugs you will be given. There are both preventive drugs that can control vomiting before it starts, and drugs that can be used if you are already nauseated or actively vomiting. Be sure to follow the instructions carefully. Some anti-emetic drugs must be started before the chemotherapy drug is given and continued for two or three days after the chemotherapy. Some anti-emetic drugs are given by mouth, some by injection and some by suppository. Be sure you understand how to use the drugs and try not to miss a dose. If you have any questions about your anti-emetic plan, please call the health care team member who oversees your chemotherapy drugs or talk with your doctor.

## **Diarrhea**

Chemotherapy-related diarrhea may occur when drugs used to treat the tumor irritate the lining of the gastrointestinal tract. That irritation may cause your intestines to absorb fluids more slowly than they usually would, and thus, diarrhea occurs. While you have diarrhea, avoid high-fiber foods and foods that can irritate the bowel such as bran, whole grain breads, fried foods, fruit juices, milk products and coffee. Until the diarrhea slows try a diet of bananas, applesauce, toast and clear liquids. Drink plenty of fluids to prevent becoming dehydrated. Your health care team can also suggest medications to slow the diarrhea, but do not use over-the-counter medications without first talking with your team.

## **Fatigue**

The most common side effect of chemotherapy is fatigue. It is experienced by almost everyone undergoing treatment for a brain tumor. This fatigue is different from the "fatigue" you might have experienced in the past.

Treatment-related fatigue is severe, persistent and does not always follow physical activity. It can be unpredictable and emotionally overwhelming. Most telling, it is not fully relieved by rest or sleep. If you have already experienced weakness or other neurologic symptoms as a result of the tumor, the fatigue may make these symptoms more severe. There might be pharmacologic ways to combat fatigue, and it is an active area of clinical research.

The first step in managing fatigue is letting your health care team know the extent of your symptoms. There is a difference between feeling “tired” and being so exhausted you cannot get out of bed. Be sure your team understands the full extent of your symptoms. Your health care team can check to be sure that this is treatment-related fatigue and can verify there are no other underlying medical concerns causing your symptoms. From there, your team can talk with you about ways to manage your fatigue and lessen its impact on your quality of life.

### FERTILITY & FETAL INJURY

**For both males and females, concerns about fertility and the ability to start a future family must be addressed in advance of your first chemotherapy treatment.** The drugs used for chemotherapy may cause damage to an unborn fetus, damage to a child conceived during chemotherapy or damage to a child conceived within the first two years after chemotherapy (the exact time varies with the drug). Some drugs carry a greater chance of fetal injury than others.

If there is any possibility that you would like to have a child at some future point in time, please speak with your doctor **before** starting your treatments. He or she can talk with you about the drugs suggested in your treatment plan, and their potential impact on fertility or an unborn child.

There are many options for saving eggs and sperm, and for other parenthood options, but these must be planned in advance.

## OTHER CHEMOTHERAPY DELIVERY METHODS

There are several other approaches to delivering chemotherapy. Not all of these are considered “standard” methods of delivering drugs, but they do represent innovative ways of bringing drugs closer to the tumor. The use of drugs targeted to specific molecular differences in tumor cells is rapidly moving forward.

### **Blood-brain barrier disruption**

Treating brain tumors with chemotherapy is different than treating tumors elsewhere in the body. The brain has a natural defense system not present in your other organs. That system, called the blood-brain barrier, protects the brain by acting as a filter. This works to our advantage when harmful substances, such as certain chemicals or bacteria, are kept out of the brain. It works to our disadvantage when substances we want to enter the brain, such as chemotherapy drugs, are filtered out.

Some drugs pass through the blood-brain barrier. Nitrosoureas (such as BCNU and CCNU) are such drugs, as well as procarbazine and temozolomide (Temodar) and methotrexate (MTX). Studies continue to explore other standard drugs, as well as new drugs, for their ability to penetrate this protective barrier.

Some tumors are behind this barrier or have cells that have moved into regions of normal brain tissue. For a drug to be effective in treating these brain tumors, a sufficient quantity must either pass through

the blood-brain barrier or bypass it entirely. Although it remains experimental, blood-brain barrier disruption is a technique used to temporarily disrupt this barrier in order to allow chemotherapy to flow into the brain.

During blood-brain barrier disruption, a drug called **Mannitol** is used to temporarily “open” the barrier. Very high-doses of chemotherapy drugs are then injected into an artery or a vein. The drug travels through the blood, through the blood-brain barrier and into the tumor area. The barrier is restored naturally as the effects of the Mannitol wear off.

Researchers are looking into new ways of opening the barrier and the most effective dose of drug to use once the barrier is open. For example, ultrasound and laser ablation techniques are areas of active study.

Blood-brain barrier disruption has been used mainly to treat primary central nervous system lymphoma and high-grade astrocytoma tumors, although the superiority of this technique over conventional treatments has not been proven.

### **Blood or marrow stem cell transplantation**

One of the more common side effects of chemotherapy is damage to the bone marrow, the part of the body that produces new blood cells. The possibility of bone marrow damage limits the amount of drug that can be given.

Doctors can now preserve immature blood cells, called stem cells, and give them back to

the patient following their chemotherapy. This procedure is called a “**stem cell transplant.**” An *autologous* transplant means the patient’s own stem cells will be used. An *allogenic* transplant uses stem cells from a donor.

Prior to chemotherapy, stem cells are collected, or “harvested,” from the donor’s circulating blood. They can also be collected from the pelvic bone, but the use of blood instead of bone marrow is becoming more common. Researchers are also exploring new sources of obtaining stem cells, such as fat cells and skin cells, but this is still experimental.

Following the harvesting of the stem cells or marrow cells, an intensive course of chemotherapy is administered over several days. After therapy is complete, the stem cells are given to the patient through an intravenous solution. During the next ten days, the stem cells begin to mature and reproduce, re-supplying the body with healthy blood cells. Drugs are given to suppress the body’s tendency to reject the new cells, and growth factors can be used to boost the growth rate of the new cells.

Because of the possibility of the body rejecting the new stem cells and the risks of intensive chemotherapy, stem cell and bone marrow transplants are used only in select circumstances. Transplants should be done at experienced institutions with a multidisciplinary team. The team can assist with donor matching, supportive counseling, family member housing during treatment and financial counseling.

**Convection enhanced delivery (CED)**

One of the newer methods of delivering drugs to a tumor is “convection enhanced delivery,” or CED. CED uses the principles of constant pressure to “flow” or “infuse” substances through brain tumor tissue. The procedure begins with surgery, during which a catheter (a tube), or multiple catheters, depending on the tumor size, is placed into the tumor area. The neurosurgeon then connects a pump-like device to the catheter, filling it with the therapeutic substance to be delivered to the tumor. The fluid flows, by use of pressure and gravity, through the tumor tissue. This “bulk flow” or “convective-delivery” method bypasses the blood-brain barrier, placing the therapeutic substance in direct contact with tumor tissue.

Clinical trials are exploring the use of CED as a way of placing chemotherapy drugs, immunotoxins and radioactive monoclonal antibodies at the tumor site.

As this technique is developing, researchers are simultaneously exploring ways to include “tracers” in the substances flowing into the brain. Those tracers can be viewed on an MRI scan performed during CED, and may allow real-time observations of the movement of therapeutic substances in and around the tumor. Research is also underway to predict the flow pattern that will occur after catheter placement.

**High-dose chemotherapy**

Some scientists believe that higher doses of chemotherapy drugs may cross the blood-

brain barrier more effectively than lower drug doses spread over a longer treatment period. “High-dose chemotherapy” involves the administration of massive doses of chemotherapy drug, followed by an antidote, which reverses the effect of the drug on normal cells. Methotrexate is the drug most often used for high-dose chemotherapy, and leucovorin is the most common antidote. This technique has been offered to those with primary central nervous system lymphomas or high-grade astrocytomas. It is sometimes combined with a stem cell transplant.

### **Intracavitary/polymer wafer implants/ interstitial therapies**

When treatment is delivered into the cavity created by the removal of the tumor, it is known as intracavitary (inside the cavity) therapy. These methods include implanted catheters and **polymer wafer implants** placed during surgery. Intracavitary techniques have the potential advantage of reducing the amount of drug affecting normal cells in the brain and throughout the body and of increasing the amount of drug reaching tumor cells.

Surgery is typically performed to remove as much of the tumor as possible, but because the cells of a malignant tumor spread into the surrounding brain tissue, additional therapy is often needed. Placing polymer wafer implants containing the chemotherapy drug carmustine (BCNU) on the walls of the resection releases the chemotherapy into the local region. This local delivery by wafer implants, also called Gliadel wafers, limits the amount of BCNU that circulates outside the brain while delivering

a high concentration to the tumor bed. Your neurosurgeon will place up to eight wafers into the cavity, based on the size of the removed tumor. The wafers are implanted immediately after the tumor is removed, adding only a few additional minutes to the surgical procedure. The neurosurgeon then surgically closes the area, leaving the wafers to gradually dissolve over the next two to three week period. As they dissolve, BCNU is released. It is usually not necessary to remove the wafers since they are biodegradable.

### **Reservoirs and pumps**

Chemotherapy can also be delivered directly into the fluid that bathes the brain and spinal cord – the cerebrospinal fluid. This treatment is used for leptomeningeal tumors involving the ventricles or spine, and tumors that tend to “seed,” or spread, down the spine. The meninges is a thin substance that coats the brain and spinal cord. A small container system, such as an “Ommaya reservoir” or other ventricular reservoir, is surgically placed under the scalp. A tube leads from the reservoir into a ventricle of the brain.

Medications are injected via syringe into the reservoir and then the reservoir is flushed with either saline or cerebrospinal fluid. The flushing begins the flow of drug through the ventricles and lining of the spine.

Chemotherapy administered this way can be repeated on a regular schedule.

## THE DIRECTION OF DRUG RESEARCH

For years, surgery followed by radiation and/or chemotherapy were the mainstays of brain tumor treatment.

Today, however, physicians and scientists are changing the world of brain tumor treatment, most notably through targeted treatments, which are aimed at specific parts or functions of tumor cells. The goal is to interfere with and redirect the way those cell functions normally work.

Scientists now know that tumors with the same appearance under a microscope may indeed be different biologically. For example, both Tumor A and Tumor B have been determined to be glioblastomas by pathology review. Biologically, however, Tumor A may be producing more proteins or fewer enzymes than Tumor B. This biologic difference may explain why two people with the same type of tumor (such as glioblastoma) may react differently to treatment and have very different outcomes.

This new knowledge is helping researchers create therapies that target the biologic markers on the surface of tumor cells or the genetic material inside the tumor cells. As a result, there are now many new opportunities to test innovative drugs, immune therapies and drug delivery systems. These therapies use altered genes, engineered viruses and drugs packaged into molecules too small to be seen with microscopes.

## Targeted therapies

Some of the newest drugs block the growth and spread of tumor cells by interfering with the proteins that may control tumor growth.

**Monoclonal antibodies**, for example, are proteins that can locate and bind to the surface of tumor cells. There are many types of monoclonal antibodies. Some carry drugs, toxins or radioactive materials directly to tumors. Others interfere with the normal work of the tumor cells, leaving tumor cells incapable of reproducing.

Bevacizumab, also known as Avastin, is a monoclonal antibody that binds to and inhibits vascular endothelial growth factor (VEGF), a protein capable of controlling the blood supply to a tumor. Bevacizumab has been shown to reduce tumors in clinical trials in patients with regrowing glioblastomas. Some trials are also exploring bevacizumab combined with temozolomide or other drugs that may increase the treatment's effectiveness.

In some brain tumors, several cell-growth switches may be simultaneously overactive, thus requiring multiple drugs to stop tumor growth. These switches, formed by molecules called receptor tyrosine kinases (RTKs), are often mutated and hyperactive in tumor cells. A number of RTK-blocking drugs are being tested in brain tumors, including erlotinib (Tarceva) and temsirolimus (CCI-779). There are many other targeted drugs now being tested against brain tumors.

## **New drug delivery systems**

One of the greatest challenges in brain tumor treatment is knowing exactly where the tumor is located, where the borders are and how to successfully reach the site through surgery and/or drugs. Fortunately, today's therapies are being aided by state-of-the-art drug delivery systems that can pinpoint the exact location of a tumor and administer precise treatment.

Through nanotechnology, for example, tiny plastic/polymer materials are being developed for use as implants containing anticancer drugs. When the anticancer drug camptothecin (CPT) is linked to the polymer polyethylene glycol (PEG), the drug penetrates more than one centimeter into the drug implant site (10 times deeper than conventional medications).

Studies are being done on “nanobubbles” delivering the chemotherapy drug, doxorubicin, directly to cancer cells in mice. When exposed to ultrasound, the bubbles generate an echo, allowing the tumor to be imaged. The sound energy from the ultrasound then pops the bubbles and releases the drug.

## **The treatments of tomorrow**

These innovative therapies represent the efforts of thousands of scientists, all focused on finding a cure for brain tumors. In the not-too-distant future, even more sophisticated scanning will visualize the DNA and RNA inside tumor cells. We are at the cusp of finding brain tumor treatments specific to the biology of each tumor. Treatment will be

personalized not to groups of people, but to your own individual genetic makeup.

### POTENTIAL BENEFITS OF CHEMOTHERAPY

The ultimate goal of chemotherapy is to kill tumor cells, or at a minimum, to stop their growth. Sometimes the intent is to shrink a tumor so that it can be further treated or removed. Chemotherapy may also be used to make a tumor more sensitive to other treatments such as radiation therapy.

There are many benefits that can result from chemotherapy alone or combined with other treatments such as surgery or radiation.

Your doctor can tell you the goal of your treatment plan. S(he) can also help you balance the potential risks of therapy against the benefits and help you make an informed decision about your care.

### POTENTIAL RISKS OF CHEMOTHERAPY

Chemotherapy, like any treatment, carries risks. Some of these are the more common side effects already discussed. Others are more rare and apply to anyone going through chemotherapy. Those rarer risks include interactions with other drugs, infertility, damage to an embryo or fetus, seizures, weakness, balance or coordination difficulties, memory or cognitive problems, brain swelling, damage to other internal organs, stroke, or very rarely, coma or death. Some forms of chemotherapy may possibly prevent your future participation in research studies. Your doctor can tell you if the drug/treatment methods suggested for you fall into this area.

## HOW TO KNOW IF CHEMOTHERAPY IS EFFECTIVE

At periodic intervals, your doctor will order follow-up MRI or CT scans to be done while you are going through chemotherapy and for a year or two after. It may take a few rounds of chemotherapy, however, before the size of your tumor begins to look smaller on your scans. Sometimes the reduction in tumor size is very dramatic and happens quickly, while sometimes it takes a few months. Stable size to a previously growing tumor can also indicate the drug is working. If your tumor size does not reduce as much as your doctor might like, there are other drugs and other treatments that may be chosen as alternatives.

## RECOVERY FROM CHEMOTHERAPY

Any treatment is a trauma to your body. Because each of us heals at our own pace, some people will recover faster than others. While there is no “normal” recovery period that applies to all people, your recovery time will depend on the following:

- Drug/s used to treat your brain tumor
- Method used to deliver the drug/s
- Effect of the drug/s on your general health

Ask your doctor to consider your treatment plan and your general medical health, and tell you what you can expect as a reasonable recovery time. This will help you set realistic goals for yourself in the weeks to months following chemotherapy.

## AMERICAN BRAIN TUMOR ASSOCIATION INFORMATION, RESOURCES AND SUPPORT

### BROCHURES

Educational brochures are available on our website or can be requested in hard copy format for free by calling the ABTA. Most brochures are available in Spanish, with exceptions marked with an asterisk.

### GENERAL INFORMATION

About Brain Tumors: A Primer for Patients and Caregivers

Brain Tumor Dictionary\*

Brain Tumors Handbook for the Newly Diagnosed\*

Caregiver Handbook\*

### TUMOR TYPES

Ependymoma

Glioblastoma and Anaplastic Astrocytoma

Medulloblastoma

Meningioma

Metastatic Brain Tumors

Oligodendroglioma and Oligoastrocytoma

Pituitary Tumors

### TREATMENT

Chemotherapy

Clinical Trials

Conventional Radiation Therapy

Proton Therapy

Stereotactic Radiosurgery\*

Steroids

Surgery

# AMERICAN BRAIN TUMOR ASSOCIATION INFORMATION, RESOURCES AND SUPPORT

## INFORMATION

ABTA WEBSITE | [ABTA.ORG](https://abta.org)

Offers more than 200 pages of information, programs, support services and resources, including: brain tumor treatment center and support group locators, caregiver resources, research updates and tumor type and treatment information across all ages and tumor types.

## EDUCATION & SUPPORT

- **ABTA Educational Meetings & Webinars**  
In-person and virtual educational meetings led by nationally-recognized medical professionals.
- **ABTA Peer-to-Peer Mentor Program**  
Connect with a trained patient or caregiver mentor to help navigate a brain tumor diagnosis.
- **ABTA Connections Community**  
An online support and discussion community of more than 25,000 members.
- **ABTA CareLine**  
For personalized information and resources, call 800-886-ABTA (2282) or email [abta cares@abta.org](mailto:abta cares@abta.org) to connect with a CareLine staff member.

## GET INVOLVED

- Join an ABTA fundraising event.
- Donate by visiting [abta.org/donate](https://abta.org/donate).

## CONTACT THE ABTA

CareLine: 800-886-ABTA (2282)

Email: [abta cares@abta.org](mailto:abta cares@abta.org)

Website: [abta.org](https://abta.org)







# AMERICAN BRAIN TUMOR ASSOCIATION

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Email: [abta-cares@abta.org](mailto:abta-cares@abta.org)



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