

A Patient Guide to Chemotherapy

General Information

Chemotherapy denotes the treatment of brain tumors with medication that is either toxic to tumor cells or kills them through interaction with receptors that induce 'programmed cell death' or prevent cell division. Chemotherapy is provided to over three-quarters of patients with malignant brain tumors. Less commonly treated are low-grade but symptomatic tumors that can not be surgically removed prior to or following radiation therapy.

Chemotherapy is usually given in cycles. A period of drug administration is followed by a resting period after which the cycle starts over again. Typically, a chemotherapy cycle lasts 4 to 6 weeks.

The chemotherapy dose is calculated based on your height and body weight. If you are given chemotherapy by mouth you will likely have to take a combination of pills of different strength to make up for the correct dose.

Chemotherapy is not only toxic to tumor cells. Adverse reactions usually affect cells of the body that have a rapid turnover such as blood cells and cells of the gastrointestinal tract.

Possible adverse reactions include:

- **Drop in red blood cells (*anemia*)**. You may feel fatigued and get short of breath with exercise that you would usually tolerate without any difficulty. A medication called erythropoietin may be prescribed to shorten the recovery from the drop in red blood cells.
- **Drop in white blood cells**. You may be more susceptible to infections. If you have a fever or cold-like symptoms that do not resolve after a couple of days please notify your doctor. Your doctor may prescribe a medication called filgrastim to increase your white blood cell count.
- **Drop in blood platelets**. You may notice that you get bruises more easily than usual, your gums bleed when you brush your teeth or that you have nosebleeds. Notify your doctor immediately.
- **Hair loss**. Most chemotherapy regimens for primary brain tumors do not make you lose your hair. You will lose hair though in the area of brain radiation.
- **Nausea and vomiting**. You will be given a medication prior to each chemotherapy application. This usually prevents nausea very effectively. Notify your doctor if you suffer from nausea that does not respond to the medication.
- **Diarrhea**. Some of the chemotherapy regimens for primary brain tumors cause diarrhea. You will be given medication to counteract this effect.
- **Allergic reaction**. As with any other kind of medication there is a potential risk of an allergic reaction. If you notice a skin rash, dizziness, swallowing or breathing

problems while on chemotherapy notify your doctor immediately. Please do not just stop the treatment on your own without telling your doctor since you may have reacted to a different medication or food.

- **Food intolerance.** With some chemotherapy drugs you have to avoid certain types of food. You will be given a detailed list by your doctor if applicable.
- **Interactions with other drugs.** Please provide your doctor with a complete list of medication including vitamins, 'alternative' cancer treatments, and 'over-the-counter' medication. Do not start yourself on medication such as cold medicine since, in rare instances, serious interactions with chemotherapy drugs may exist
- **Hearing loss.** This is a rare occurrence with chemotherapy for most primary brain tumors. Typically, your doctor will obtain a hearing test prior to chemotherapy with a drug that may have this side effect.
- **Kidney or liver failure.** These are rare side effects of chemotherapy for primary brain tumors. You may require blood draws at scheduled intervals to monitor your kidney and liver function.
- **Teratogenicity.** It is mandatory that you practice effective birth control while you are receiving chemotherapy. **Do not try to conceive a child while on chemotherapy.** Severe damage to the unborn child may occur.
- **Sterility.** Sterility after chemotherapy is rare but its occurrence is unpredictable. It is strongly recommended that men who need to undergo chemotherapy and plan to have children afterwards deposit a sperm specimen at a 'sperm bank'. Information and appointment scheduling for this service at Yale School of Medicine, Department of Obstetrics & Gynecology is available at (203) 785 5525.
- **Pulmonary Fibrosis.** A cumulative side effect of some chemotherapeutic agents is 'stiffening' of the lungs. This only occurs after a certain cumulative dose which is only rarely reached in the treatment of primary brain tumors. Your doctor may order a special lung scan to determine if early damage is present.
- **Peripheral neuropathy.** Some chemotherapy drugs (such as vincristine) can cause nerve damage. Your dose may have to be reduced if you develop early signs of nerve damage (tingling or numbness in fingertips and toes). The so called autonomic nerves (the nerves that innervate blood vessels and the intestines) can be affected as well. You may experience belly pain or dizziness when you get up to fast.
- **Other types of cancer.** Secondary malignancies, frequently affecting blood cells, can occur in 5-10 % of patients treated with certain chemotherapy agents.

Please notify your doctor immediately if you experience any side effects that you relate to the chemotherapy. You may need scheduled blood draws during each chemotherapy cycle. Usually you can have blood drawn at a local laboratory. Ask the laboratory to fax a copy of the result report to your doctors' office at (203) 785 2042. Call your doctor or our clinical coordinator no later than one day after the blood draw to discuss the results.

Tumor cells can grow resistant to chemotherapy. Your doctor will obtain MRI scans on a regular basis to monitor the efficacy of treatment. If the tumor starts growing back in spite of chemotherapy, the treatment will need to be changed to a drug with a different 'attack' mechanism.

Specific types of Chemotherapy

Alkylating agents

The group of so called ,alkylating agents' targets the genetic information of the tumor cell, the DNA.

Temozolomide [Temodar]

Temozolomide is a relatively new chemotherapy drug. It is given by mouth, usually as a combination of pills of different strengths. Temodar comes in four different strengths [250 mg, 100 mg, 20 mg, 5 mg]. Each chemotherapy cycle with Temodar lasts 4 weeks. The treatment is given on the first five days followed by a resting period of 23 days. Other schedules exist such as daily low-dose temozolomide during radiation therapy for malignant gliomas.

The most common side effects are fatigue, mostly during the days of drug treatment, nausea and a drop in white blood cells and blood platelets. Blood draws are required on day #21 and day #28 of each cycle or weekly if you receive temozolomide daily during radiation.

Zofran in combination with Temodar can make you constipated. It is advised to take an over the counter laxative such as Senna prophylactically.

PCV (Combination chemotherap with procarbazine, lomustine (,CCNU') and vincristine)

PCV is commonly used in oligodendrogliomas and oligoastrocytomas. Procarbazine and lomustine [CCNU] are ,alkylating' agents attacking the DNA of tumor cells whereas vincristine is a ,spindle toxin' that inhibits proteins that are essential for cell division.

Procarbazine is given by mouth. Tablet strength is 50 mg. You will be prescribed to take two or three tablets on day #8 to #21. Procarbazine can cause sterility. Male patients should ask their doctor about the possibility of storing a sperm specimen in the Yale Sperm Bank.

Procarbazine, an inhibitor of monoamine oxidase, cannot be used concomitant with certain antidepressants or tyramine-rich food or alcohol.

As a general rule, you should always notify your doctor if you need any type of medication (including **any** over the counter medication !!!) while on procarbazine, five days before it is started and five days after the end of the two week period of drug administration.

Lomustine [CCNU] is given by mouth on day one. It comes in capsules of different strengths. You will likely take a combination of pills. The most common side effects are a drop in blood cell counts, and nausea/vomiting.

Vincristine is given as an injection or short infusion on day #8 and day #28. You will see your doctor and have blood drawn prior to each administration. You should always plan to have somebody drive you to your appointment. Acute side effects are rare (abdominal discomfort) but could potentially interfere with your ability to drive.

Many other chemotherapeutic drugs are used for the treatment of tumors of the nervous system. A detailed description of these drugs would go beyond the scope of this website. Below you will find general information on commonly used drugs. You will receive more specific information from your doctor if applicable.

Carmustine [BCNU]

Carmustine has a similar mechanism of action as lomustine. Both drugs have represented the major chemotherapy agents provided for malignant glioma. It is usually given as an intravenous infusion every six weeks. BCNU is toxic to bone marrow precursors of blood cells, lung, liver and kidney. BCNU is the chemotherapeutic agent used in implantable wafers [Gliadel®].

Cyclophosphamide

Cyclophosphamide can be administered by vein or by mouth. It is used for the treatment of systemic lymphoma and primitive neuroektodermal tumors (see Introduction to Brain Tumors).

Antifolates

Methotrexate

Methotrexate is a potent inhibitor of dihydrofolate reductase (DHFR), an enzyme that catalyzes the synthesis of carrier molecules needed for the synthesis of nucleic acids (the molecules that form the DNA, the genetic information). It is used in the treatment of primary brain lymphoma and primary sarcomas of the nervous system.

Cytosine Arabinoside

Molecules analogous to nucleic acids – the molecules that form the DNA – interfere with the replication of DNA, a step that is indispensable for cell proliferation. Cytosine arabinoside (Ara-C) is a commonly used agent belonging to this group of agents. It is given into a vein or directly into the spinal fluid for lymphoma of the nervous system.

Antimicrotubule Agents

Division of tumor cells can be inhibited by Vinca alkaloids (e.g., vincristine). They are naturally found in *Catharanthus roseus*. Vinca alkaloids are administered by intravenous injection or short infusion for patients with gliomas or primitive nerve neuroektodermal tumors.

Compounds based on elemental platinum

Platinum compounds (cisplatin, carboplatin, oxaliplatin) bind to DNA and thus inhibit DNA reduplication and cell proliferation. They are used for the treatment of glioma, medulloblastoma, primitive neuroektodermal tumor and germ cell tumors.

Topoisomerase inhibitors

DNA, the chemical basis of genetic information, is a dynamic molecule that coils and bends within the nucleus of each cell. These coils and bends must be temporarily unwound in order for the tumor cell to be able to replicate the genetic information and then divide. This process is facilitated by enzymes called topoisomerase I and II. Pharmacological inhibition of these enzymes can be used to treat cancer of the brain. Drugs that inhibit topoisomerases were found in plant extracts. The ones in use today mostly are derivatives of the original compounds chemically modified to increase their efficacy and decrease toxicity.

Irinotecan

Irinotecan is a semisynthetic derivative of camptothecin, an alkaloid extract from certain plants. Various dosing schedules exist. Most commonly, irinotecan is given every three weeks as an intravenous infusion or once every week for four weeks followed by a break of two weeks. It is used for the treatment of malignant gliomas.

semisynthetic derivatives of podophyllotoxin, a substance found in mayapple extracts, inhibit the relegation of DNA from the cleavage complex. As mentioned above, DNA intercalators such as anthracyclines interfere with the formation of the cleavage complex.

Etoposide

Etoposide is a semisynthetic derivative of podophyllotoxin, a substance found in mayapple extracts. It is being used as part of multi-drug regimens against a large number of primary brain tumors. It is given as an infusion several days in a row followed by two to three weeks rest or daily as a tablet.

Strategies of Treatment Delivery

The brain is very well protected from potentially damaging organisms or substances circulating with the blood stream and even from an attack from the body's immune system. The protective mechanisms that under normal circumstances prevent damage from the nervous system, represent a major obstacle if there is a disease such as a brain tumor within the brain. Several strategies have been developed to circumvent this barrier.

Intrathecal Administration of Chemotherapy

Injection of chemotherapy into the 'subarachnoid' space [intra-thecal chemotherapy] is necessary when systemic cancer (such as lung or breast cancer) or, less commonly, cancer of the brain spreads to the fluid surrounding the brain, the cerebrospinal fluid.

Three drugs are available for this application: methotrexate, cytosine-arabioside and thio-TEPA. Drugs are injected up to twice weekly. This can be done through a catheter that is introduced in one of the fluid filled spaces of the brain and attached to a permanent reservoir that is placed by a neurosurgeon underneath the scalp (Ommaya reservoir). If only few injections are necessary, chemotherapy can be injected through a lumbar puncture (placement of a needle into the spinal fluid surrounding the lower spinal cord in the lower back). Possible side effects include headache, nausea, vomiting, or seizures. Steroids by mouth (Decadron) may be prescribed prophylactically.

Intraarterial chemotherapy

Chemotherapy is usually given by vein or by mouth. Alternatively, it can be injected into an artery that supplies the cancer with blood. This strategy is still being evaluated in clinical trials for its usefulness in the treatment of primary brain tumors.

Biodegradable polymers impregnated with chemotherapy

Dime-sized wafers of a polymer impregnated with the chemotherapeutic agent BCNU can be placed within the cavity that surgery leaves behind in the brain. Their use is still limited by penetration of the chemotherapy drug over only a short distance into the brain. Future developments based on this principle may prove more efficacious.

High-dose chemotherapy

Therapeutic concentrations of certain chemotherapy drugs such as methotrexate within the brain can be achieved by giving them into a vein at high doses.

Other drugs can only be given at high doses if it is followed by a bone marrow transplantation. This approach, though successful for other types of cancer, has not resulted in a better outcome in most primary brain tumors.