Cyclophosphamide Fact Sheet

(sye-kloe-FAHS-fah-mide)

Generic Name: Cyclophosphamide
Trade Name(s): Cytoxan®, Neosar® (Procytox, Canada)

Drug Type:
Cyclophosphamide is an anti-cancer (antineoplastic or cytotoxic) chemotherapy drug and is classified as an alkylating agent. Alkylating agents are compounds that work by adding an alkyl group to the guanine base of the DNA molecule, preventing the strands of the double helix from linking as they should. This causes breakage of the DNA strands, affecting the ability of the cancer cell to multiply. Cyclophosphamide is a mustard gas derivative. Mustard gas was used as a lethal gas in World War I. After World War I, medical researchers noticed an interesting effect of mustard gas—it destroyed lymphatic tissue and bone marrow. They reasoned that perhaps, it could also kill cancer cells in the lymph nodes. At the start of World War II, the U.S. government asked Yale to study chemical warfare agents. Building on research that had languished for years, two scientists (Goodman and Gilman) found in a derivative of mustard gas the first alkylating agent, which became an effective chemotherapy for cancer. Based on this discovery, cyclophosphamide was developed in the 1950s.

What Conditions Are Treated by Cyclophosphamide?
Cyclophosphamide is FDA-approved for treatment of Hodgkin's and non-Hodgkin's lymphoma, Burkitt's lymphoma, chronic lymphocytic leukemia (CLL), chronic myelocytic leukemia (CML), acute myelocytic leukemia (AML), T-cell lymphoma (mycosis fungoides), multiple myeloma, neuroblastoma, retinoblastoma, rhabdomyosarcoma, Ewing's sarcoma, breast, testicular, endometrial, ovarian, and lung cancers, and in conditioning regimens preparing patients for bone marrow transplantation.

When cyclophosphamide is combined with other drugs, the combination becomes a more effective therapy. Cyclophosphamide may be combined with the monoclonal antibody rituximab for the treatment of Waldenstrom's macroglobulinemia (WM). If dexamethasone is added, the regimen is known as DRC (dexamethasone, rituximab, and cyclophosphamide), CDR, or RCD. This DRC regimen was evaluated in a study of 72 previously untreated WM patients. An overall response rate of 83% was observed. The median time for a patient to respond was long, about four months, which suggests that this combination is not the best to use if rapid control of disease is necessary. Toxicities with DRC were mild, with the only moderate to severe toxicity being neutropenia in 9% of patients. This study was recently updated, showing a time to disease relapse of 35 months. The majority of relapsing patients were still sensitive to rituximab-based therapies. Long-term toxicities, including transformation to aggressive disease or to myelodysplasia, were low. This combination has become widely used as first-line and relapse therapy in the treatment of WM and is one of the preferred regimens in both settings, according to the NCCN® Guidelines and the IWWM Consensus Panel Treatment Recommendations. It can be helpful in frail patients requiring combination therapy.

If cyclophosphamide is combined with hydroxydaunorubicin, Oncovin (vincristine), and prednisone it is called CHOP and if rituximab is added, it is referred to as CHOP-R or R-CHOP. It can be used as first-line and relapse therapy but is not a preferred regimen in the NCCN® Guidelines or the IWWM Consensus Panel Treatment Recommendations. Because vincristine is associated with a high risk of peripheral neuropathy, cyclophosphamide-based regimens without vincristine may be preferred.

The combination of fludarabine, cyclophosphamide and rituximab (called FCR) is effective in WM with rapid, high response rates and median progression-free survivals in some studies exceeding 50 months. However, due to the potential toxicities to stem cells from fludarabine in this combination, FCR is not a preferred regimen

in the NCCN® Guidelines or the IWWM Consensus Panel Treatment Recommendations in either first-line or relapse settings, although it can be used as an alternate option in patients with high-risk disease who are not candidates for autologous stem cell transplant. In patients who are eligible for autologous stem cell transplant, stem cells should be collected before fludarabine administration. Cyclophosphamide alone does not appear to harm stem cell collection and can therefore be used in patients who may be candidates for autologous stem cell transplant. More information about stem cell transplantation can be found in a separate Fact Sheet on the IWMF website at www.iwmf.com/publications. Prophylaxis to prevent *Pneumocystis* pneumonia and herpes zoster (shingles) should be seriously considered for patients on FCR.

How Does Cyclophosphamide Work?
Cancer cells no longer have the normal checks and balances in place that control and limit cell division. The ability of cyclophosphamide to kill cancer cells depends on its ability to halt cell division. Usually, the drug works by damaging the RNA or DNA that tells the cell how to copy itself in division. If the cells are unable to divide, they die. The faster the cells are dividing, the more likely it is that chemotherapy will kill the cells. Cyclophosphamide can also induce cell suicide (self-death or apoptosis). The scheduling of chemotherapy is based on the type of cancer cells (in WM, it is the lymphoplasmacytic lymphoma LPL cells), the rate at which they divide, and the time at which a given drug is likely to be effective. Therefore, chemotherapy is typically given in cycles.

Unfortunately, cyclophosphamide does not differentiate between the cancer cells and normal cells when killing rapidly dividing cells. The normal cells will grow back and be healthy but, in the meantime, side effects can occur. The normal cells most affected by this drug are blood cells, the cells in the mouth, stomach and bowel, and the hair follicles – resulting in low blood counts, mouth sores, nausea, diarrhea, and/or hair loss, respectively.

How Is Cyclophosphamide Given?
Cyclophosphamide can be given as an infusion into a vein (intravenous, IV) or by mouth in tablet form. Tablets should be given with foods or after meals. Tablets should not be crushed or cut.

The administration route depends on the dosage, the condition being treated, and the purpose for which it is being used. It is also approved for injection into a muscle (IM), into the abdominal or stomach area lining (intraperitoneal, IP), or into the lining of the lung (intrapleural).

The amount of cyclophosphamide that is prescribed depends on many factors, including the patient's height, weight, and blood counts, general health (including other health problems), and the type of cancer or condition being treated, in this case WM. The health care team will determine the dose, schedule and route of administration.

Cyclophosphamide Side Effects:
The side effects of cyclophosphamide and their severity depend on how much of the drug is given. High doses may produce more severe side effects. Most people will not experience all the side effects listed in this fact sheet. Side effects are often predictable in terms of their onset, duration, and severity. They are almost always reversible and will go away after therapy is completed.

The following cyclophosphamide side effects are common and temporary (occurring in greater than 30% of patients): low blood counts (red cells, white cells, and platelets), thereby increasing the risk for infection, anemia, and/or bleeding. Low blood counts begin at about 7 days after the start of therapy, reach their lowest point at 10-14 days, and recover at about 21 days after the initiation of therapy. Hair loss may be temporary, usually begins 3-6 weeks after the start of therapy, and grows back after treatment is completed, although the color and texture

may be different. Nausea and vomiting are more common with larger doses, usually beginning 6-10 hours after therapy. Poor appetite, loss of fertility, and discoloration of the skin and nails are also common side effects.

The following are less common side effects (occurring in about 10-30% of patients): diarrhea, mouth sores, and bladder problems, such as bladder irritation and bleeding (hemorrhagic cystitis).

There is a slight risk that long-term use of cyclophosphamide can damage the DNA of blood-forming stem cells, leading to the development of a second blood cancer, such as leukemia or myelodysplasia. This risk should be discussed with the health care team.

When Should a Health Care Provider Be Contacted?
Contact a health care provider immediately, day or night, if experiencing any of the following symptoms: fever of 100.5° F (38° C) or higher or chills (both are possible signs of infection).

The following symptoms also require medical attention. Contact the health care team if experiencing any of the following: nausea, vomiting (more than 4-5 times in a 24-hour period), diarrhea (4-6 episodes in a 24-hour period), unusual bleeding or bruising, black or tarry stools or blood in your stools, blood in your urine, pain or burning with urination, extreme fatigue (unable to carry on self-care activities), or mouth sores (painful redness, swelling, and ulcers).

Before starting cyclophosphamide treatment, make sure to tell the health care team about any other medications being taken. While taking cyclophosphamide, do not take aspirin or products containing aspirin unless the health care team specifically permits this. The interaction of cyclophosphamide and other medications, including aspirin, can increase or decrease the amount of cyclophosphamide in the blood, causing either too much drug (toxicity) or not enough drug and inadequate killing of cancer cells.

Do not receive any kind of immunization or vaccination without the health care team's approval while on cyclophosphamide. For both men and women: use contraceptives, and do not conceive a child (get pregnant) while taking cyclophosphamide. Barrier methods of contraception, such as condoms, are recommended. Do not breast feed while taking this medication.

Always inform the health care team if you experience any unusual symptoms.

What are Some Self-Care Tips While Taking Cyclophosphamide?
While taking cyclophosphamide, try to drink at least two to three quarts of fluid every 24 hours, unless instructed otherwise by the health care team.

It is particularly important to void (empty) your bladder frequently, especially in the first 24 hours after taking cyclophosphamide. Report any pain or burning upon urination to the health care team.

The risk of infection increases while taking cyclophosphamide, so try to avoid crowds or people with colds and report fever or any other signs of infection immediately to the health care team. Wash your hands often.

To help treat/prevent mouth sores, use a soft toothbrush and rinse three times a day with 1 teaspoon of baking soda mixed with 8 ounces of water.

Use an electric razor and a soft toothbrush to minimize bleeding. Avoid contact sports or activities that could cause injury.

To reduce nausea, take anti-nausea medications as prescribed by the health care team and eat small, frequent meals while taking cyclophosphamide. In general, drinking alcoholic beverages should be kept to a minimum or avoided completely.

Avoid sun exposure. Wear SPF 15 (or higher) sun block and protective clothing. Get plenty of rest and maintain good nutrition. If symptoms are noted or side effects experienced, be sure to discuss them with the health care team. They can prescribe medications and /or offer other suggestions that are effective in managing such problems.

How is Monitoring and Testing Done While Taking Cyclophosphamide?
Patients taking cyclophosphamide are checked regularly by the health care team to monitor side effects and check response to therapy. Periodic blood work will be obtained to monitor the complete blood count (CBC) as well as the function of other organs, such as the kidneys and liver.

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About the IWMF
The International Waldenstrom's Macroglobulinemia Foundation (IWMF) is a patient-founded and volunteer- led, nonprofit 501(c)(3) organization with an important vision, "A World Without WM," and a mission to "Support and educate everyone affected by WM while advancing the search for a cure."

More information about Waldenstrom's macroglobulinemia and the services and support offered by the IWMF and its affiliate organizations can be found on our website, www.iwmf.com.
The IWMF relies on donations to continue its mission, and we welcome your support. The Foundation maintains a Business Office at 6144 Clark Center Ave., Sarasota, FL 34238. The Office can be contacted by phone at 941-927-4963, by fax at 941-927-4467, or by email at info@iwmf.com.