Cyclophosphamide: Clinical Insights

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Cyclophosphamide (Cytoxan) is a potent non-cell-cycle-specific alkylating agent related to nitrogen mustard and has activity against many types of cancers. With Ifosfamide and Trofosfamide, cyclophosphamide belongs to the family of oxazophorines.

Cyclophosphamide is used in the treatment of many types of cancers including:

- Breast cancer
- Non-Hodgkin’s disease
- Chronic lymphocytic leukemia
- Ovarian cancer
- Bladder cancer
- Multiple myeloma
- Mycosis fungoides
- Leukemia
- Bone and soft tissue sarcoma
- Rhabdomyosarcoma
- Neuroblastoma
- Wilm's tumor

In addition to the above anti-tumor treatments, cyclophosphamide has other uses in clinical practice. Cyclophosphamide is commonly used in the setting of hematopoietic stem cell transplant to mobilize stem cells from the bone marrow to peripheral circulation. Cyclophosphamide is also used to suppress host immune system to prevent graft rejection in patients who have received organ transplants. Cyclophosphamide is used in several auto-immune diseases including lupus, rheumatoid arthritis, Wegener’s granulomatosis, and nephritic syndrome in children.

Description

Cyclophosphamide for injection is a white powder containing cyclophosphamide monohydrate, which makes a colorless solution when dissolved. This drug is usually administered intravenously. It is also available as a white colored 25 mg or 50 mg tablet for oral use. A port-a-cath or PICC line is commonly used to administer cyclophosphamide intravenously.

Metabolism and Mechanism of action

Cyclophosphamide is inactive in its parent form and it has to be metabolized to active forms before this drug can exert its cytotoxic effects. Metabolism of cyclophosphamide occurs mainly in liver, but may also occur in other tissues as well. Enzymatic breakdown of cyclophosphamide by cytochrome P450 results in various products with cytotoxic activity. Most important of these are phosphoramid mustard, and acrolein. Phosphoramid mustard is responsible for the anti-tumor effects of cyclophosphamide, while acrolein is responsible for bladder toxicity and is also responsible for causing hemorrhagic cystitis that is often seen with high dose cyclophosphamide treatment. Phosphoramid mustard interacts with DNA producing DNA cross-links through linkage of highly reactive alkyl groups. Highly reactive phosphoramid mustard reacts with the N7 of guanine residues in DNA to form a covalent bonding. Meanwhile the second arm of the phosphoramid mustard reacts with a second guanine moiety of an adjacent DNA strand or in the same strand to form inter-strand and intra-strand DNA crosslinks. Crosslink formation makes the DNA dysfunctional by preventing replication and modulation of cell cycle. The cell harboring this damaged DNA in turn will undergo apoptosis and die.

Side effects

Hypersensitivity reactions:
Cyclophosphamide may be associated with hypersensitivity. Serious hypersensitivity reactions including anaphylaxis and death may occur during administration of cyclophosphamide. Patients who have developed hypersensitivity reactions to
cyclophosphamide in the past should not receive the drug again.

**Bone marrow suppression:** Treatment using cyclophosphamide may lead to severe bone marrow suppression and immunosuppression. This may predispose the patient to serious and sometimes fatal bacterial, viral and fungal infections. Patients who are receiving cyclophosphamide should be closely monitored. Some patients may require antibacterial, antiviral and antifungal prophylaxis. Patients with significant neutropenia as defined by absolute neutrophil count of less than 1500 should not receive cyclophosphamide treatment. White cell growth factors like Filgrastim or Peg-Filgrastim are often administered following cyclophosphamide treatment to prevent or reduce the intensity of neutropenia. This is called primary prophylaxis. If patient is found to be trending towards neutropenia, these patients are more effectively treated with Filgrastim in secondary prophylaxis. Treatment using cyclophosphamide may also result in thrombocytopenia and or anemia. These patients may require transfusion support. Patients with metastatic disease who develop chemotherapy induced anemia may be treated with Epoetin Alfa to reduce transfusion requirements. Nadir of blood counts is usually reached around day-10 post chemotherapy, following which the counts usually start recovering and normalize in around day-20. In some patients, especially in those receiving concurrent radiation therapy and cyclophosphamide chemotherapy bone marrow failure may occur, leading to prolonged cytopenia and risk of infections and transfusion requirements.

**Bladder toxicity:** Cyclophosphamide may cause bladder toxicity and this may manifest in various ways including, hemorrhagic cystitis and urinary infections. Occasionally hemorrhagic cystitis may become very severe and protracted and may need surgical intervention. Acrolein, which is a metabolite of cyclophosphamide, is responsible for bladder toxicity including hemorrhagic cystitis. High dose cyclophosphamide treatment is associated with increased risk of bladder toxicity. Hemorrhagic cystitis may result in ulceration, fibrosis and contracture of the bladder and this in turn acts as a risk factor for the development of bladder cancer. It is very important to ensure there is no urinary obstruction, before administration of cyclophosphamide. Extreme caution should be used if this drug is used in patients with active urinary infection. Measures to reduce bladder toxicity include aggressive hydration and frequent bladder emptying during the treatment. Mesna is often used prevent severe bladder toxicity. Treatment using cyclophosphamide may lead to microscopic and gross hematuria, which usually occur within forty eight hours after treatment.

**Cardiotoxicity:** Treatment using cyclophosphamide may be associated with significant cardiac toxicity and may lead to myocarditis, pericarditis, cardiac tamponade and congestive heart failure. High-dose cyclophosphamide may result in acute form of cardiotoxicity within days of treatment. The acute form of cardiotoxicity may last from one to six days. This is associated with high mortality rate, however if the patient survives the acute event, there are no late sequels associated with this condition. The risk of developing cardiotoxicity may be higher in elderly patients, patients who had previous radiation therapy to mediastinum, and patients who received higher dose of the drug. Concurrent use of other cardiotoxic drugs like doxorubicin also increases the risk of cardiac toxicity. Complications like cardiac arrhythmias including QT prolongation, atrial fibrillation, atrial flutter and ventricular arrhythmias might develop following cyclophosphamide treatment. Extreme caution should be used in patients who have preexisting cardiac disease or any of the risk factors mentioned above.

**Pulmonary Toxicity:** Cyclophosphamide induced lung toxicity is relatively rare. Risk of developing pulmonary toxicity is higher with concurrent use of radiation therapy or drugs that are known to cause lung toxicity.
Treatment using cyclophosphamide may result in various forms of lung toxicity including pneumonitis, pulmonary veno-occlusive disease, and pulmonary fibrosis. Lung toxicity may lead to respiratory failure. Lung toxicity may take an acute or late form of onset. Late onset lung toxicity is associated with increased morbidity and mortality. Patients may develop lung toxicity, years after their exposure to cyclophosphamide and this should be kept in mind while following these patients on a long term basis.

**Veno-occlusive Disease of Liver (VOD):** VOD is more commonly associated with administration of high dose chemotherapy in the setting of stem cell transplant. VOD is associated with high risk of mortality and this is a major cause of morbidity and mortality in patients receiving allogenic stem cell transplantation. Use of a preparatory regimen consisting of cyclophosphamide has been identified as a major risk factor for development of VOD. This disorder is also known to be associated with chronic long term immunosuppressive doses of cyclophosphamide as well. Preexisting liver disease and prior radiation to abdomen are risk factors for development of VOD.

**Development of secondary Malignancies:** Cyclophosphamide is carcinogen and treatment using cyclophosphamide is associated with increased risk of developing secondary malignancies like urinary tract cancers, MDS, acute leukemia, lymphoma, thyroid cancer, skin cancer and sarcoma. Patients who have developed hemorrhagic cystitis have a significantly high risk of developing bladder cancer. Risk of development of malignancy is dose depended with patients who have received higher doses bearing higher risk. Cyclophosphamide causes DNA damage by crosslinks and this increases the chance for DNA mutations which in turn increases the risk of cancers.

**Teratogenic effects:** Cyclophosphamide is a teratogen and is known to cause Embryo-Fetal Toxicity. Administration of cyclophosphamide to pregnant women may cause birth defects, miscarriages and fetal growth retardation. This drug should be avoided in pregnancy especially during the first trimester. Women of childbearing age should be strongly warned not to become pregnant while on treatment. Cyclophosphamide induced fetal toxicity is usually manifested as abnormalities of central nervous system, skeletal, and facial anomalies.

**Nausea and vomiting:** Treatment with cyclophosphamide either as single agent or in combination treatment may be associated with significant nausea and vomiting. Cyclophosphamide causes nausea and vomiting by activating the chemoreceptor trigger zone (CTZ) resulting in the release of various neurotransmitters causing stimulation of vomiting center. Nausea and vomiting are generally controlled by 5-HT3 antagonists like ondansetron given prior to administration of cyclophosphamide.

**Alopecia:** Patients who receive cyclophosphamide may experience alopecia. Alopecia usually starts about 4-5 weeks from administration of the first dose of the drug, which may get worse during the next few courses of treatment. In most patients the alopecia is temporary and the hair will grow back once the chemotherapy is completed.

**Diarrhea:** Patients who are treated with cyclophosphamide may experience varying degrees of diarrhea. Diarrhea is usually mild and can usually be easily controlled with anti-motility drugs. Patients should be advised to replace the water loss, so that they do not get dehydrated during episodes of diarrhea. If patients develop severe diarrhea, inpatient hydration may be required.

**Mucositis:** Development of mucositis may be associated with cyclophosphamide therapy. This usually occurs during second or third week of treatment. Mucositis predisposes patient to development of bacterial and fungal infections. Ulceration may not be limited to oral cavity, but other areas of the gastro-
intestinal tract may also be involved in the process of mucositis. Ulcerations of the intestine may resolve in most cases, but occasionally may progress to necrosis and gangrene. This possibility should be kept in mind while following patients on treatment using cyclophosphamide.

**Impairment of Fertility:** Both male and female reproductive function could be adversely affected by cyclophosphamide. Cyclophosphamide interferes with production of sperms as well as ova. Administration of cyclophosphamide may lead to sterility in male as well as in female. Patients who received higher doses of cyclophosphamide are at higher risk of developing sterility. Prolonged low dose treatment using cyclophosphamide may also lead to sterility. Some patients may regain fertility after stoppage of treatment, but majority of patients will not recover reproductive function once it is lost.

**Breast feeding:** Cyclophosphamide may appear in breast milk following administration to the mother. Breastfeeding while mother is on active treatment using cyclophosphamide may result in severe neutropenia and thrombocytopenia in infants. These infants may also develop Immunosuppression and may become susceptible to infections. Also to be remembered that cyclophosphamide is a carcinogen. Breast feeding is contra-indicated while a nursing mother is on treatment using cyclophosphamide.

**SIADH:** Treatment using cyclophosphamide may lead to syndrome of inappropriate antidiuretic hormone (SIADH), which will present as water overload and hyponatremia. One single dose of cyclophosphamide may precipitate SIADH in some patients. SIADH may cause severe hyponatremia, which must be corrected slowly. Rapid correction of hyponatremia may result in central pontine myelinolysis. Even low dose treatment using cyclophosphamide may lead to development of SIADH.

**Impairment of wound healing:** Cyclophosphamide administration may lead to impairment of wound healing. Hence this drug should be avoided close to surgery. Give enough time for wound healing prior to administration of cyclophosphamide.

**Use in special population**

**Use in liver impairment:** Since cyclophosphamide is metabolized mainly through liver. Patients with severely impaired liver function may not be able to convert cyclophosphamide to its active metabolites and this may result in decreased efficiency of the drug.

**Use in patients with impaired renal function:** Patients with severe renal dysfunction may have impaired excretion of cyclophosphamide. This may result in accumulation of the drug in the plasma, subsequently leading to increased drug toxicity. This drug should be used with caution in patients with severe renal impairment. Cyclophosphamide and its metabolites are removed through dialysis hence if given to patients on dialysis, a consistent interval between cyclophosphamide administration and dialysis should be maintained.

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http://medicineworld.org/cancer/breast/treatment/chemodrugs/cytoxan.html
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