Cyclophosphamide

Cyclophosphamide is an alkylating agent, which works by cross-linking DNA at the guanine N7 position, causing cell apoptosis. Before becoming active, cyclophosphamide is bioactivated by cytochrome P450 in the liver. It is used for a variety of disorders, including lymphomas, such as Hodgkin's and non-Hodgkin's lymphoma, along with various leukemias. It is used to treat solid malignancies, such as breast, ovarian, cervical, testicular cancers, along with soft-tissue sarcomas. Furthermore, it can aid in treatment of autoimmune disorders, such as SLE, rheumatoid arthritis, multiple sclerosis, as well as amyloid-light chain amyloidosis. Cyclophosphamide has important side effects you should know; myelosuppression, leading to decreased red and white cells, along with thrombocytes. Another highly tested side effect is hemorrhagic cystitis, which can be treated with Mesna. Another pearl is that cyclophosphamide use has been associated with SIADH (syndrome of inappropriate diuretic hormone).

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Mechanism

Requires Bioactivation by Liver
Bioactivating Liver
It is important to know that cyclophosphamide requires bioactivation by the liver before having its therapeutic effects. As a prodrug, it is converted by liver cytochrome P450 (CYP) enzymes to form the metabolite 4-hydroxy cyclophosphamide that has chemotherapeutic activity.

Cross-links DNA
Linked DNA
Cyclophosphamide is an alkylating agent, meaning it works by cross-linking DNA. It does so because alkylating agents add an alkyl group to DNA, and specifically, cyclophosphamide adds an alkyl group at the guanine N7 position. Once DNA is cross-linked, it is inhibited from replicating.

Guanine N7 Position
G-iguana in N7 Position
This alkylating agent adds an alkyl group to the guanine base pair at the number 7 nitrogen atom of the imidazole ring, specifically. Thus, it is said that this drug alkylates, and leads to cross-links at the guanine N7 position.

Indications

Autoimmune Disorders
Auto-in-moon
Because cyclophosphamide depresses leukocyte replication, this medication can be used for various autoimmune disorders. This includes rheumatoid arthritis, SLE, and multiple sclerosis. It can be used for autoimmune vasculitis disorders, such as microscopic polyangiitis and polyarteritis nodosa. Cyclophosphamide can also be used for minimal change disease.

Leukemia
Leukemia-Luke
This drug is used to treat various leukemias, such as chronic lymphocytic leukemia and chronic granulocytic leukemia (it is usually ineffective in acute blastic crisis). It is also used for acute myelogenous and monocytic leukemia, acute lymphoblastic (stem-cell) leukemia in children (Cyclophosphamide given during remission is effective in prolonging its duration).

Lymphoma
Lime-foam
Cyclophosphamide is one of the drugs used to treat lymphomas such as Hodgkin's and non-Hodgkin's lymphomas including Burkitt's lymphoma.

Solid Tumors
Tumor-guy
This drug is used for various solid tumors, such as breast cancers, ovarian and cervical cancers, and testicular cancers. It can be used for soft-tissue malignancies (sarcomas).

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Side Effects

Myelosuppression

Suppressed Red and White blood cells

This medication can cause bone marrow toxicity, which can manifest as myelosuppression. This can lead to decreased erythrocytes (RBCs), leukocytes (WBCs), and thrombocytes (platelets) in patients. This is due to the fact that this drug interferes with DNA replication.

Hemorrhagic Cystitis

Bladder with Hemorrhage-hammer

A highly tested side effect of cyclophosphamide use is the development of hemorrhagic cystitis. Cyclophosphamide causes the chemical acrolein to be produced, and acrolein is toxic to the bladder epithelium (leading to hemorrhagic cystitis). Patients display microscopic or gross hematuria and occasionally dysuria. Risks of hemorrhagic cystitis can be minimized with adequate fluid intake, avoidance of nighttime dosage, and mesna, which binds and detoxifies acrolein. It should also be noted that this drug is associated with an increased incidence of transitional cell carcinoma (TCC).

Prevent with Mesna

Prevented with Mesh-knot

Remember that Mesna is a highly tested treatment for the side effect of hemorrhagic cystitis associated with this medication's use. Mesna binds to acrolein, a toxic metabolite of cyclophosphamide, working to inhibit the hemorrhagic cystitis that can develop in patients. Other mitigating precautions patients can take include adequate hydration and avoiding nighttime dosing of this medication.

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