Purine Antagonists Pharmacology

Purines are chemicals that are used to build the nucleotides of DNA and RNA. They include **adenine** and **guanine**. The other class of base, the pyrimidines, are represented in DNA by thymine and cytosine and in RNA by cytosine and uracil.

Before a cell undergoes cell division, first it has to duplicate its DNA content, so that each daughter cell has a complete and identical set of genetic information. During this duplication process, phosphate groups and sugar molecules join together to form the long strands of DNA found in our chromosomes.

The incorporation of a purine antagonist prevents the continued growth of the DNA and prevents cell division.

Purine antagonists **work by inhibiting DNA synthesis** in two different ways:

First is by **inhibiting production of the purine containing nucleotides, adenine and guanine.** If a cell doesn't have sufficient amounts of purines, DNA synthesis is halted and the cell cannot divide.

Secondly, they may be **incorporated into the DNA molecule during DNA synthesis**. The presence of the inhibitor is thought to interfere with further cell division.

Purine antagonists that are used to treat cancer patients include **6-mercaptopurine** (6-MP) and **6-thioguanine** (6-TG). These agents are similar to each other, and work in the same way. The structures the normal purines (adenine and guanine) with their antagonists (6-MP and 6-TG)

Examples of purine antagonists used to treat cancer include:

6-Mercaptopurine
Dacarbazine
Fludarabine

6-Thiopurines

6-Mercaptopurine (6-MP)

6-Mecarptopurine is the **first of the thiopurine analogs** that was found to be effective in cancer chemotherapy. 6-MP is inactive in its parent form and has be metabolized by an enzyme known as **hypoxanthine-guanine phosphoribosyl transferase (HGPRT)** to the monophosphate nucleotide 6-thioinosinic acid, which then in turn inhibits several enzymes of de novo purine nucleotide synthesis.

There is a formation of other cytotoxic metabolites such as **thioguanylic acid** and **6-methylmercaptopurine ribotide (MMPR)** from 6-MP.

6-MP is used primarily in the treatment of childhood **acute leukemia**, and a closely related analog, azathioprine that is used as an immunosuppressive agent.

6-Thioguanine (6-TG)

6-Thioguanine works by **inhibiting a number of enzymes in the de novo purine nucleotide biosynthetic pathway**. Various metabolic lesions result, including inhibition of purine nucleotide interconversion; decrease in intracellular levels of guanine nucleotides, which leads to inhibition of glycoprotein synthesis; interference with the formation of DNA and RNA; and incorporation of thiopurine nucleotides into both DNA and RNA.

6-TG has a synergistic action when used together with cytarabine in the treatment of **adult acute leukemia.**

Dosage and Toxicity

6-MP and 6-TG are both given orally and excreted mainly in the urine.

However, 6-MP is converted to an inactive metabolite (6-thiouric acid) by an oxidation catalyzed by xanthine oxidase, whereas 6-TG requires deamination before it is metabolized by this enzyme.

This factor is important because the purine analog allopurinol, a potent xanthine oxidase inhibitor, is frequently used with chemotherapy in hematologic cancers to prevent hyperuricemia after tumor cell lysis. It does so by blocking purine oxidation, allowing excretion of cellular purines that are relatively more soluble than uric acid.

Nephrotoxicity and acute gout produced by excessive uric acid are thereby prevented. Simultaneous therapy with allopurinol and 6-MP results in excessive toxicity unless the dose of mercaptopurine is reduced to 25% of the usual level. This effect does not occur with 6-TG, which can be used in full doses with allopurinol.

Fludarabine

Fludarabine (2-fluoro-ara-AMP) is an analogue of adenosine. Fludarabine phosphate is rapidly dephosphorylated in the plasma to 2-fluoro-arabinofuranosyladenosine and then phosphorylated intracellularly by deoxycytidine kinase to the triphosphate form.

The triphosphate metabolite interferes with the processes of DNA synthesis and DNA repair through **inhibition of DNA polymerase- and DNA polymerase- .**

This false nucleotide also **inhibits ribonucleotide reductase and DNA polymerase,** resulting in the inhibition of DNA synthesis.

The triphosphate form can also be directly incorporated into DNA, resulting in inhibition of DNA synthesis and function.

The diphosphate metabolite of fludarabine inhibits ribonucleotide reductase, leading to inhibition of essential deoxyribonucleotidetriphosphates.

Finally, fludarabine **induces the process of apoptosis** through as yet undetermined mechanisms.

Fludarabine is used chiefly in the treatment of **low-grade non-Hodgkin's lymphoma and chronic lymphocytic leukemia (CLL).**

It is given parentally and is excreted primarily in the urine; its dose-limiting toxicity is myelosuppression.

In addition, this agent is a potent **immunosuppressant** with inhibitory effects on CD4 and CD8 T cells.

Patients are at increased risk for opportunistic infections, including fungi, herpes, and Pneumocystis jiroveci.

Cladribine

Cladribine (2-chlorodeoxyadenosine) is a purine nucleoside analog with high specificity for lymphoid cells.

Inactive in its parent form, it is initially phosphorylated by deoxycytidine kinase to the monophosphate form and eventually metabolized to the triphosphate form, which can then be incorporated into DNA.

The triphosphate metabolite can also **interfere with DNA synthesis and DNA repair by inhibiting DNA polymerase- and DNA-polymerase-** , respectively.

Cladribine is indicated for the treatment of **hairy cell leukemia,** and it also has activity in **CLL** and **low-grade non-Hodgkin's lymphoma.**

It is normally administered as a single continuous 7-day infusion; under these conditions, it has a very manageable safety profile with the main toxicity consisting of transient myelosuppression.

it has immunosuppressive effects, and a decrease in CD4 and CD8 T cells, lasting for over 1 year, is observed in patients.