Pyrimidine Antagonists Pharmacology

The pyrimidine antagonists are a class of cancer chemotherapy drugs that work by blocking the synthesis of pyrimidine containing nucleotides (C and T in DNA; C and U in RNA). These drugs are used to block the construction of these nucleotides. They have structures that resemble with the natural compound. Therefore by acting as 'decoys', they can prevent the production of the finished and functional nucleotides.

Pyrimidine antagonists may exert their effects at different steps in that pathway and may directly inhibit crucial enzymes in the cells. They may also be incorporated into a growing DNA chain and lead to termination of the process.

In the normal cell physiology, we know that, for a cell to reproduce, it must first faithfully replicate all of the DNA in its genome. During the process of DNA synthesis, pyrimidine and purine molecules must be available to allow for the synthesis of the nucleotide building blocks and ultimately synthesis of new DNA molecules.

With the action of pyrimidine antagonists, there is a reduced availability of these raw materials that are needed to build DNA material, leading to stoppage of DNA synthesis and inhibition of cell division.
Cancer cells have the ability to divide rapidly and therefore they are more engaged in the DNA synthesis.RNA synthesis is necessary for the process of protein production. Therefore, pyrimidine antagonists inhibit this normal processes of DNA and/or RNA synthesis in cancer cells.

Examples of pyrimidine antagonists used in cancer therapy include:

- 5-fluorouracil
- Arabinosylcytosine
- Capecitabine
- Gemcitabine
- Decitabine

5-Fluorouracil

5-Fluorouracil (5-FU) is a prodrug that requires activation via a complex series of biotransformation reactions to ribosyl and deoxyribosyl nucleotide metabolites. One of these metabolites that is, 5-fluoro-2'-deoxyuridine-5'-monophosphate (FdUMP), forms a covalently bound ternary complex with the enzyme known as thymidylate synthase and the reduced folate

N-methylenetetrahydrofolate. This reaction is critical for the de novo synthesis of thymidylate.

This process results in the inhibition of DNA synthesis through a process known as "thymineless death."

5-FU is then converted to 5-fluorouridine-5'-triphosphate (FUTP), which is incorporated into RNA,

where it interferes with RNA processing and mRNA translation.

In addition, 5-FU is converted to 5-fluorodeoxyuridine-5'-triphosphate (FdUTP), which can be incorporated into cellular DNA, resulting in inhibition of DNA synthesis and function. Thus, the cytotoxicity of5-FU is thought to be the result of the combined effects on both DNA- and RNA-mediated events.

5-FU is normally administered intravenously and has a half-life of 10–15 minutes.

It is not administered by the oral route because its bioavailability is impaired by the high levels of the breakdown enzyme dihydropyrimidine dehydrogenase that is present in the gut mucosa.
Up to 80–85% of an administered dose of 5-FU is catabolized by this enzyme.

5-FU is the most widely used agent in the treatment of colorectal cancer, both as adjuvant therapy and for advanced disease.
In addition, it has activity against a wide variety of solid tumors, including breast cancer, stomach, pancretic cancer, esophagus, liver, head and neck, and anus.

Capecitabine

Capecitabine is a fluoropyrimidine carbamate prodrug with nearly 70–80% oral bioavailability. It undergoes extensive metabolism in the liver by the enzyme carboxylesterase to an intermediate, 5'-deoxy-5-fluorocytidine. This, in turn, is converted to 5'-deoxy-5-fluorouridine by the enzyme cytidine deaminase.

The 5'-deoxy-5-fluorouridine metabolite is then hydrolyzed by thymidine phosphorylase to 5-FU directly in the tumor. The expression of thymidine phosphorylase has been shown to be significantly higher in a broad range of solid tumors than in corresponding normal tissue. Peak plasma levels are achieved in about 1.5 hours, and peak 5-FU levels are reached at 2 hours after oral administration.

Capecitabine is used in the treatment of metastatic breast cancer either as a single agent or in combination with the taxane docetaxel. It is also approved for use in the adjuvant therapy of stage III colon cancer as well as for treatment of metastatic colorectal cancer as monotherapy.

The main toxicities of capecitabine include diarrhea and the hand-foot syndrome. While myelosuppression, nausea and vomiting, and mucositis can also be observed with this agent, the incidence is significantly less than that seen with intravenous 5-FU.

Cytarabine

Cytarabine (cytosine arabinoside, ara-C) is an S phase-specific antimetabolite that is converted by deoxycytidine kinase to the 5'-mononucleotide (ara-CMP). Ara-CMP is further metabolized to the triphosphate ara-CTP, which competitively inhibits DNA polymerase- and DNA polymerase- , thereby resulting in blockade of DNA synthesis and DNA repair, respectively.

Cytarabine is also incorporated into RNA and DNA. Incorporation into DNA leads to interference with chain elongation and defective ligation of fragments of newly synthesized DNA. The cellular retention time for ara-CTP appears to correlate with its lethality to malignant cells.

After intravenous administration, the drug is cleared rapidly, with most of an administered dose being deaminated to an inactive form.

In view of cytarabine's S phase specificity, the drug is highly schedule-dependent and must be given either by continuous infusion or every 8–12 hours for 5–7 days. Its activity is limited exclusively to hematologic malignancies, including acute myelogenous leukemia and non-Hodgkin's lymphoma. It has absolutely no activity in solid tumors.

Gemcitabine

Gemcitabine is a deoxycytidine analog that is phosphorylated initially by the enzyme deoxycytidine kinase to the monophosphate form and then by other nucleoside kinases to di- and triphosphate nucleotide forms.

The antitumor effect is considered to result from two different mechanisms:

Inhibition of ribonucleotide reductase by gemcitabine diphosphate, which reduces the level of deoxyribonucleoside triphosphates required for DNA synthesis;

Incorporation of gemcitabine triphosphate into DNA, leading to inhibition of DNA synthesis and function. Following incorporation of gemcitabine nucleotide, only one additional nucleotide can be added to the growing DNA strand, resulting in chain termination.

Gemcitabine was initially approved for use in pancreatic cancer but is now widely used in the treatment of non-small cell lung cancer, bladder cancer, and non-Hodgkin's lymphoma. Myelosuppression in the form of neutropenia is the principal dose-limiting toxicity.