Page 585 to 587

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The Medicinal Value of Pyrimidines Structural Similarity, But Different Mechanisms and Clinical Applications

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An old-recent question;" Does structural similarity exactly reflect the same mechanism of action and clinical application?" Brief discussion of the medicinal value of some pyrimidine analogues, generally classified as antimetabolites may provide an answer.

Pyrimidines and purines have long beem discovered. [1,2] such molecules make living creatures' life possible being the basic constituents of DNA and RNA. Uracil, its 6-methyl analogue (thymine), its 4-amino analogue (cytosine) are pyrimidine derivatives, while adenine and guanine are imidazolopyrimidine derivatives (Chart 1).

That is, simply pyrimidine ring is the highest common factor, constituting more than 70% of the living creatures' genetic materials. Perhaps, this is one of the factors that explain the tremendous clinical applications of Pyrimidines as therapeutic agents. Literature [3] indicates diverse medicinal use of pyrimidine derivatives including the anticancer, antibacterial, antiviral, antifungal, anti- inflammatory, anti-allergic, and anti-diabetic, antihypertensive, and GABARs, GlyRs modulators.

Azacitidine®, Decitabine®, Cytarabine® and Gemcitabine® (chart 1) are cytosine analogues, but have different mechanisms [4,5] and clinical applications as antineoplastic antimetabolites, interfering or competing with nucleoside triphosphates required for the synthesis of DNA or RNA or both. However, the first two drugs behave uniquely by blocking or inhibiting the DNA methyl transferase and mostly used for the treatment of Myelodysplastic syndrome. Cytarabine [6] is one of the cytosine group, but the sugar moiety is unique being arabinose in which the 2'-hydroxy is in β-configuration. Its mode of action is due to fast conversion into cytosine arabinoside triphosphate, which damages DNA when the cell cycle holds in the S phase (synthesis of DNA). It is used to treat different types of Leukemia and non-Hodgkin's lymphoma.

The fourth analogue of cytosine group, Gemcitabine® [7] acts by incorporating into cell's DNA creating an irreparable error that leads to inhibition of further DNA synthesis and consequently cell death. Clinically, Gemcitabine® is used to treat breast, ovarian, non-small cell lung, pancreatic and bladder cancer.

In contrast, Uracil analogues, 5-fluorouracil® (5-FU) [8] and Floxuridine® [9] have more typically antineoplastic activity and are important agents in regimens for several solid tumors. 5-FU inhibits thymidylate synthetase, thus blocking the synthesis of thymidine, which is needed for DNA replication. Floxuridine® interferes with DNA synthesis and to lesser extent inhibits RNA formation through its

incorporation into RNA, forming "fraudulent" RNA. Finally, Capecetabine® [10] is used to treat breast, gastric and colorectal cancer. It is metabolized to 5-FU which is thymidylate synthetase inhibitor, hence inhibiting the synthesis of thymine monophosphate which is needed for the de novo synthesis of DNA.

In conclusion, chemical structural similarity is not, by necessity, leads to identical mechanisms of action or the same clinical use.

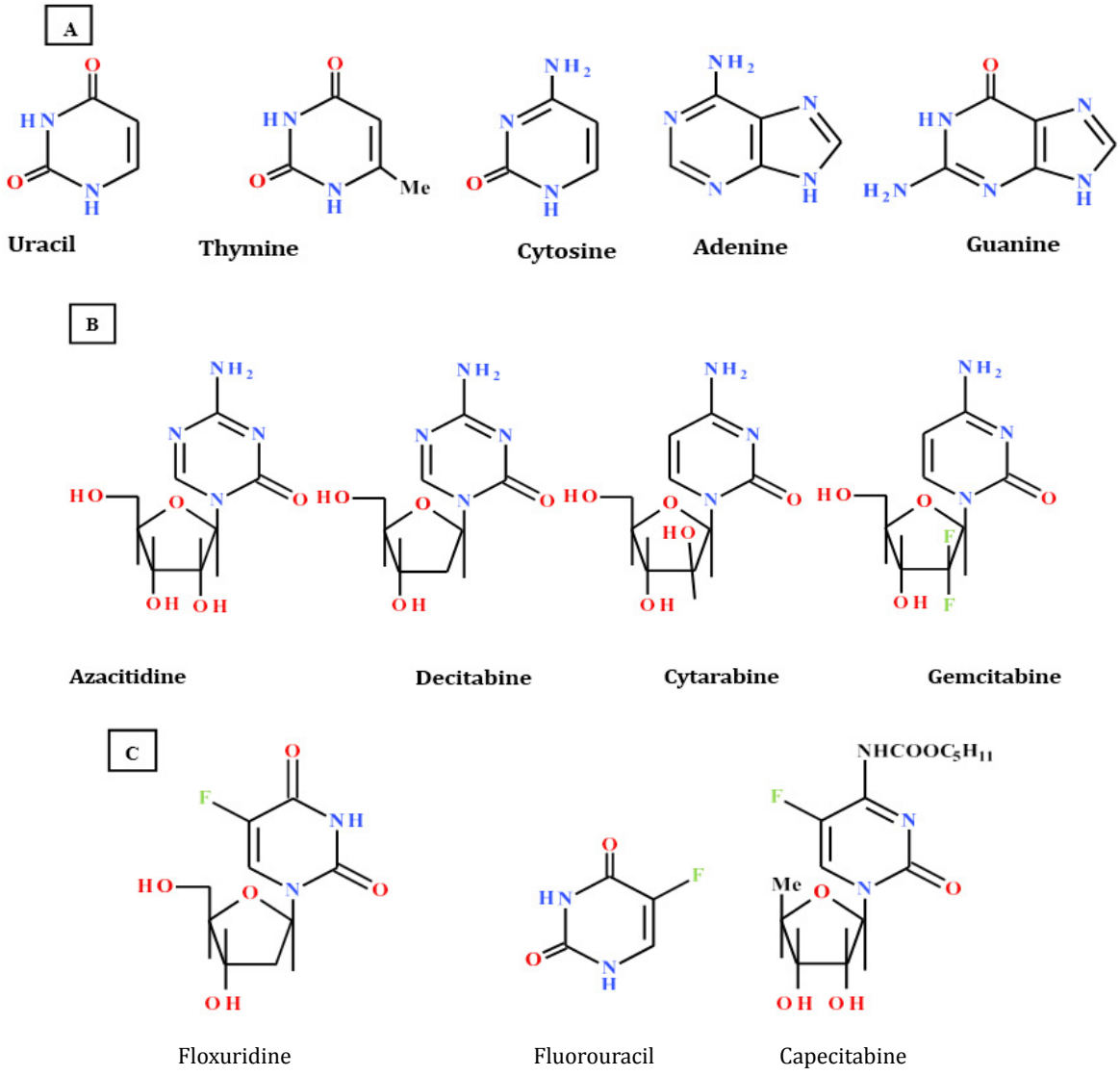

Chart 1: ***A:*** *Natural bases* ***B:*** *Cytosine analogues anticancer drugs*

C: *Uracil analogues anticancer drugs*

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