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News & Comments

Potential Side Effects of Certain Cancer-treating Drugs

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Hepatoma, or liver cancer, is a type of cancer that develops in the liver. Secondary liver cancer is cancer that has spread to the liver from somewhere else. Every cell has proto-oncogenes, which are cancer-causing genes that are dormant. These proto-oncogenes can be awakened by a variety of triggering agents (chemical, physical, or biological) that modify and turn them into oncogenes; these triggering agents are known as carcinogens. Various innovative approaches for the treatment of liver cancer, such as epidermal growth factor receptors [gefitinib, erlotinib], antibodies targeting Haemoglobin derived Growth Factor (HGF) (bevacizumab), and target tyrosine kinase Furthermore, platinum-based compounds are used in a variety of pharmacological regimens and are the mainstay of treatment. Sorafenib is a drug that is commonly used in the treatment of liver cancer. However, these medications have potentially serious negative effects.

Researchers must discover a novel anticancer agent that can treat cancer with minimal risk of damage, due to the potential side effects and economic burden of currently existing medications. Because cancer cells grow faster than normal tissues, methotrexate may reduce uncontrolled and undesirable development while avoiding irreversible damage to normal tissues. When evaluating the risk-benefit ratio of modern anticancer medications, it may be concluded that they still lack specificity and are associated with higher toxicities. The purpose of this study was to see how G6PD and DHFR affected DENA-induced hepatocarcinogenesis in rats.

The Department of Pharmacology, Pharmacology and Toxicology Laboratory, College of Pharmacy, Jouf University, Aljouf, KSA, conducted all the experiments. DENA was acquired from Sigma Aldrich, USA, whereas primaquine and methotrexate were purchased from Carbosynth Limited, Berkshire, UK. (Applied Biosystems, UK), reverse transcription kit (High-capacity cDNA) and PCR Master Mix (SYBR1 Green), reagent TRIzol (Life Technologies, Grand Island, USA). A total of 30 Albino Wistar rats (6-7 weeks) were obtained from the College of Pharmacy's animal care section at Jouf University in Saudi Arabia. Rats were randomly assigned to one of five groups (n = 6): Normal Saline (NS) was served to Group 1 for 21 days as a control group. Group 2 was designated as a hazardous group and was exposed to DENA (200 mg kg^{-1}) during the treatment period.

In DENA-induced cancer in rats, we discovered that combination therapy with G6PD and DHFR inhibitors (Primaquine+Methotrexate) produces consistent and excellent results. HCC was the third most predictable cause of cancer-related death. DENA is a hepatotoxin that has been shown to harm hepatocytes in animal models. The severity of hepatocyte injury was determined by using blood markers ("DENA-exposed animals had higher levels of α-fetoprotein, ALP, ALT, and AST. Serum concentrations are higher "Western blot study of inflammation-induced proteins confirms that α-fetoprotein represents a

malignant state. The current study found that DENA treatment produces hepatocyte damage that progresses to HCC, which can be easily linked to significantly up-regulated serum liver enzymes and "α-fetoprotein levels.

The results of the western blot assay show that DENA administration in animals increased NF-κB and Bcl-2 protein expressions and decreased its inhibitory protein IkB-α," whereas treatment with methotrexate and primaquine alone and in combination significantly reduced elevated levels of NF-α κB and Bcl-2 and restored the inhibitory protein IkB-α," with the combination showing the most promising results.

The entire economic impact of HCC, as well as it's high prevalence, has prompted scientists to look for new medicines to treat it. The lack of selective medications for the treatment of HCC, as well as the potential side effects of current combination therapy, paves the way for the development of more selective and efficacious pharmacotherapeutic regimens for HCC. The current study found that treatment regimens containing methotrexate (a dihydrofolate reductase inhibitor) and primaquine (a glucose-6-phosphate dehydrogenase inhibitor) are more effective in preventing the de-novo production of DNA nucleotides.

JOURNAL REFERENCE

Alharbi, K.S., M. Afzal, I. Kazmi, S.I. Alzarea and N.H. Alotaibi *et al.*, 2022. Protective effect of glucose-6-phosphate dehydrogenase and dihydrofolate reductase against diethylnitrosamine-induced hepatocellular carcinoma in rats. Int. J. Pharmacol., 18: 354-362.