DOI : 10.35124/bca.2020.20.1.2091

Biochem. Cell. Arch. Vol. 20, No. 1, pp. 2091-2099, 2020 | www.connectjournals.com/bca | *ISSN 0972-5075*

6-MERCAPTOPURINE DERIVATIVES : MAINTENANCE THERAPY OF ACUTE LYMPHOBLASTIC LEUKEMIA: A REVIEW

Shams A. Nadhum*, Rana A. Kamoon and Mohammed H. Mohammed

Department of Pharmaceutical Chemistry, College of Pharmacy, University of Baghdad, Baghdad, Iraq.
*e-mail: shams_an10@yahoo.com

(Received 18 June 2019, Revised 3 September 2019, Accepted 12 September 2019)

ABSTRACT : Six-mercaptopurine (6-MP) is used in the maintenance therapy of acute lymphoblastic leukemia (ALL) and it also displays activity against acute and chronic myelogeneousleukemias. The clinical use of the thiopurines against solid tumors has been limited by severe bone marrow toxicity. But there are several drawbacks such as toxicities, lack of selectivity and effectiveness as well as the development of resistance that need to be overcome. In this review, the latest innovations in 6-MP derivatives drug are presented. Moreover, advances to overcome or determine 6-MP adverse effects and effectiveness are described. Although in the past few years there has been a great advancement in the antitumor effectiveness and selectivity of 6-MP-based therapies. This review shows that 6-MP derivatives or 6-MP based therapies tailored to individual patients opens up new possibilities in the improvement of the quality of life and survival for those suffering from this devastating disease.

Key words : 6-MP, 6-MP Prodrug, thiopurine derivative, cytototoxicity.

INTRODUCTION

The design of new anticancer therapies focus on the design of new derivatives of existing drugs to overcome adverse side effect and resistance of currents treatments opened a new anticancer therapies. In 1953 at the United States, 6-MP was approved for medical use (Hayhoe, 1955). It was the most effective and safe medicines on the World Health Organization's List of Essential Medicines needed in a health system (WHO, 2015). It was used for cancer and autoimmune diseases medication (Hayhoe, 1955). It was used to treat acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML), Crohn's disease (CD) and ulcerative colitis specifically (Hayhoe, 1955; Danese, 2011). Among the most commonly used immunosuppressive drugs to treat Crohn's disease symptoms were the thiopurine drugs and its metabolite 6-mercaptopurine (6-MP). They induce and maintain Crohn's disease remission (Travis *et al*, 2006). The deficiency or complete lack of enzyme hypoxanthine guanine-phosphoribosyltransfersae (HGPRT) caused resistance to the thiopurines drug (Relling *et al*, 1998), which was linked to the increased levels of glutathione (Gunnarsdottir *et al,* 2004). Mercaptopurine toxicity can be linked to genetic polymorphisms in thiopurine *S*-methyltransferase (TPMT), nudix hydrolase 15 (NUDT15) and inosine triphosphate pyrophosphatase (ITPA) (Yang *et al*, 2015; Moriyama *et al*, 2016), which led to the development of new 6-MP derivatives. Pharmacological properties of 6-MP can be improved by improving selectivity toward cancer cells and increasing specific tumor cell toxicity and decreasing resistance. 6-MP derivatives in the form of prodrugs have been created to achieve this target (Mohammed *et al*, 2012; Johnston *et al*, 1985). The modifications of 6-MP consist of conjugation with nucleotide, which was tested for cytotoxic and/or growth inhibitory effects against MP-sensitive and -resistant cell culture lines (Johnston *et al*, 1985).

This review gives an overview of the latest achievements on 6-MP derivatives synthesis, the use of combined antineoplastic agents, chemotherapy, target molecules to improve 6-MP efficiency and discuss from a clinical point of view the new advances to overcome 6-MP adverse effect and highlight the main challenges to be addressed in the future.

The main mechanism of action ofMercaptopurine (6-MP) is converted to thioinosine monophosphate (TIMP) when competes with the purine derivatives hypoxanthine and guanine for the enzyme HGPRT. The conversion of inosinic acid (IMP) toxanthylic acid (XMP) and to adenylic acid (AMP) via adenylosuccinate (SAMP) are inhibited by (TIMP) chemical. In addition methylation of TIMP produce 6-methylthioinosinate (MTIMP). Both TIMP and MTIMP have been reported as inhibitors for glutamine-5-phosphoribosylpyrophosphate amidotransferase, the first enzyme unique to the *de novo* pathway for purine