Cyclophosphamide (CP), an oxazaphosphorine alkylating agent introduced in 1958, is widely used in the treatment of solid tumors and B-cell malignant disease, such as lymphoma, myeloma, chronic lymphocytic leukemia and Waldenstrom macroglobulinemia. Furthermore, CP and ifosfamide (IF), a synthetic analogue of CP, have had an increasing role in the treatment of nonneoplastic diseases, such as thrombocytopenic purpura, rheumatoid arthritis, systemic lupus erythematosis, nephritic syndrome, and Wegener granulomatosis, and as a conditioner before bone marrow transplantation [1]. Soon after their discovery, as early as 1960, the first side-effects of CP were reported by Coggins and co-workers [2]. These side-effects have been reported as transient irritative voiding symptoms, including urinary frequency, dysuria, urgency, suprapubic discomfort and strangury with microhematuria as well as life-threatening hemorrhagic cystitis. Bladder fibrosis, necrosis, contracture, and vesicoureteral reflux also have been reported [2]. Hemorrhage usually occurs during or immediately after treatment, whether with short-term high or long-term low dosages.

In 1981, Brock et al [3, 4] have documented that the urotoxicity of these cytostatics is not based on a direct alkylating activity on the urinary system but rather on the formation of 4-hydroxy metabolites, in particular, renal excretion of acrolein, which is formed from hepatic microsomal enzymatic hydroxylation. Following this discovery, experimental works have been made to elucidate how acrolein causes such a life-threatening side effect; hemorrhagic cystitis. A vast array of studies clearly showed that CP and IF-derived acrolein initiates a pathophysiological cascade beginning with oxidative [5-7] and nitrosative stress [8, 9]. Further studies indicate that a variety of cytokines [10-12], transcription factors and pro-inflammatory enzymes [9, 10, 13-15] have been involved acrolein-induced hemorrhagic cystitis. As a result, the overall mechanism appears as a well-established non-infectious inflammation [10, 16, 17].

In the current issue of the Journal of Experimental and Integrative Medicine, Ribeiro and co-workers [18], one of the leading groups in this area, extensively outlined how acrolein initiates the urological complications and all players involving the pathophysiological cascade of hemorrhagic cystitis. In this paper, acrolein-induced hemorrhagic cystitis has been perfectly explained and several cytokines and pro-inflammatory players involving the mechanism discussed in detailed [18]. We are confident that this paper will shed light on not only preventing of hemorrhagic cystitis occurrence but a vast array of other non-infectious conditions sharing with the similar pathophysiological mechanisms.

References


Key words: Cyclophosphamide; Ifosfamide; Hemorrhagic cystitis

Correspondence:
A. Korkmaz
Gulhane Askeri Tip Akademisi,
Fizyoloji Anabilim Dali,
06010 Etilk, Ankara, Turkey.
korkmaza@gata.edu.tr

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