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Thalidomide Ameliorates Cisplatin-Induced Nephrotoxicity by Inhibiting Renal Inflammation in an Experimental Model

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ABSTRACT—Cisplatin is a platinum-based chemotherapy drug. However, its chemotherapeutic use is restricted by serious side effects, especially nephrotoxicity. Inflammatory mechanisms have a significant role in the pathogenesis of cisplatin-induced nephrotoxicity. Thalidomide is an immunomodulatory and anti-inflammatory agent and is used for the treatment of various inflammatory diseases. The purpose of this study was to investigate the potential nephroprotective effect of thalidomide in a mouse model of cisplatin-induced nephrotoxicity. Nephrotoxicity was induced in mice by a single injection of cisplatin (15 mg/kg, i.p.) and treated with thalidomide (50 and 100 mg/kg/day, orally) for 4 days, beginning 24 h prior to the cisplatin injection. Renal toxicity induced by cisplatin was demonstrated by increasing plasma levels of creatinine and blood urea nitrogen (BUN). Cisplatin increased the renal production of the proinflammatory cytokines tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and transforming growth factor (TGF)-β1. In addition, kidney levels of malondialdehyde (MDA), myeloperoxidase (MPO), and nitric oxide (NO) were increased by cisplatin. Biochemical results showed that thalidomide reduced cisplatin-induced increase in plasma creatinine and BUN. Thalidomide treatment also significantly reduced tissue levels of the proinflammatory cytokines, MDA, MPO, and NO and increased anti-inflammatory cytokine IL-10. Furthermore, histological examination indicated that thalidomide ameliorated renal damage caused by cisplatin. These data suggest that thalidomide attenuates cisplatin-induced nephrotoxicity possibly by inhibition of inflammatory reactions. Taken together, our findings indicate that thalidomide might be a valuable candidate for the prevention of nephrotoxicity in patients receiving cisplatin.

KEY WORDS: cisplatin; nephrotoxicity; thalidomide; cytokines; nitric oxide.

INTRODUCTION

Cisplatin (*cis*-diamminedichloroplatinum [II]) and other platinum-containing compounds are important chemotherapeutic agents, which have been used in the treatment of various types of solid tumors, including nonsmall cell and small cell lung cancer; esophageal, gastric, and colon cancer; head and neck cancer; and genitourinary cancers, particularly ovarian, testicular, and bladder cancer [1]. The clinical use of cisplatin is often limited by its undesirable side effects. Nephrotoxicity is the most important and dose-limiting adverse effect of cisplatin which occurs in 20–30 % of patients [2]. Although there is no effective treatment for cisplatin-induced nephrotoxicity, there are various anti-inflammatory, antioxidant, and antiapoptotic agents that have been suggested to prevent cisplatin nephrotoxicity [3]. Amifostine, a thiophosphate cytoprotective agent, is approved by FDA to prevent kidney damage caused by cisplatin, but is not commonly used [4, 5]. The study of the pathogenesis of cisplatin nephrotoxicity is important for the development of new therapeutic strategies to reduce renal toxicity of cisplatin. The exact mechanisms involved in cisplatin-induced renal dysfunction are not completely understood.

Several molecular mechanisms have been proposed to be involved in the pathogenesis of cisplatin-induced nephrotoxicity such as inflammation, oxidative stress,

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