Introduction

Cisplatin (cis-diamminedichloroplatinum II, CDDP) is one of the most common anti-cancer drug in clinic which is accompanied with side effects of toxicity such as nephrotoxicity. It seems that age is an important factor influencing the side effects of CDDP. This study was designed to determine the role of age and gender simultaneously in CDDP induced renal toxicity. Methods: 40 Wistar male and female rats were assigned as 6 groups in 3 different age categories (10, 16, and 20 weeks old). The single dose of CDDP (7.5 mg/kg, ip) was administrated, and a week later measurements were performed. Results: Body weight changes in male (not in female) animals aged 16 and 20 weeks were more than 10 weeks old animals (P<0.05). In male rats, the serum levels of creatinine (Cr) and blood urea nitrogen (BUN), and Cr-clearance in aged 10 weeks, normalized kidney weight (KW) in aged 20 weeks, and serum nitrite, aspartate aminotransferase (AST) and malondialdehyde (MDA) levels and kidney tissue damage score (KTDS) in rats aged 16 weeks were significantly altered (P<0.05). Gender difference in serum level of Cr, BUN and nitrite, and Cr-clearance were observed in animals aged 10 weeks (P<0.05). Conclusion: The side effects of CDDP are gender depended, and may be different at various ages.

Keywords: Cisplatin- cancer- age- gender- Rat

Asian Pac J Cancer Prev, 18 (6), 1703-1705
The serum levels of malondialdehyde (MDA) and nitrite (Griess Method) were quantified according to the manual methodology. The left kidney was fixed in 10% neutral formalin solution and was embedded in paraffin for the histopathological staining. The hematoxylin and eosin staining was applied to examine the tubular damages. The tubular lesions were scored from 1 to 4 (in the form of a parameter named as kidney tissue damage score, KTDS) while the score of zero was assigned to normal tubes without damage. The Cr clearance was calculated based on renal clearance formula.

Data are presented as mean ± SEM. Analysis of variance (ANOVA) followed by LSD as the post hoc was applied to compare quantitative data between the groups, and the Student t-test was used to compare the data between genders. The Kruskal-Wallis and Mann-Whitney U tests were employed to compare the KTDS between the groups. P values <0.05 were considered statistically significant.

Results

The weight loss/gain induced by CDDP were 4.9±3.2, -15.1±4.9 and -13.5±5.1 g in male, and -3.3±3.7, -7.8±4.8 and -8.8±4.3 g in female, respectively in animal aged 10, 16 and 20 weeks. The weight change in 16 and 20 weeks old male (not female) rats were significantly different from younger one (P<0.05). The serum levels of Cr and BUN, and Cr-clearance in male rats aged 10 weeks were significantly different from the others older rats, while such observations were not seen in female rats. The net kidney weight (KW) after one week of CDDP therapy were 1.65±0.03, 2.02±0.09 and 2.1±0.15 g in male, and 1.36±0.05, 1.52±0.06 and 1.49±0.05 in female aged 10, 16 and 20 weeks rats respectively. The KW in 16 and 20 weeks old male (not female) rats were significantly different from younger one (P<0.05) and KW was different between sexes in each age category (P<0.05), however different result was obtained when it normalized to body weight (Figure 1). The normalized KW in 20 weeks old male (not female) rats was significantly different from younger one (P<0.05). In addition, the normalized KW in male rats treated with CDDP was significantly different from the other gender (P<0.05). The serum nitrite, MDA and AST levels and KTDS in 16 weeks old male rats were statistically different from the rats in two other categories of ages (P<0.05). The results are presented in Figure 1. Actually both age and gender influenced in CDDP induced side effects.

Discussion

The major findings of this short study indicated that the serum levels of BUN and Cr, and Cr-clearance were age and gender related, and young male animals (10 weeks old) had the lower BUN and Cr and the higher Cr-clearance responses to CDDP administration. Opposite to this finding, it is reported that increased BUN and Cr and KTDS induced by CDDP in male rats were more than in female (Nematbakhsh et al., 2013a), and possibly the difference was related to age, because in animals aged 16 and 20 weeks, almost the mean values for BUN and Cr and KTDS in male were greater than female rats (Figure 1). The higher Cr-clearance in young male rats may reveal the existence of more suitable renal blood flow when compared with the other groups. This result also is in contrast with Winston and Safirstein study that reported the reduction of renal blood flow by CDDP.

![Figure 1](image-url)
(Winston and Safirstein, 1985). In laboratory, usually adult rats (> 11 weeks old) use for animal research, and therefore the impact of age may be ignored. Nitrite and MDA alterations responses to CDDP administration were different, and they were increased in 16 weeks old rats. Nitrite increase in adult rats treated with CDDP was reported previously (Nematbakhsh et al., 2013b), and also it was considered also gender related (Taskiran et al., 1997; Watanabe et al., 2000; Ahmed et al., 2007). The liver enzymes also act differently in different ages and gender. However, there is no exact interpretation for it.

As a conclusion, cancer is a major problem in today’s society, especially at an early age in both male and female, and CDDP as anti-cancer is one of the choice by clinician for chemotherapy. Using CDDP to treat cancer in different genders and ages may be associated with different side effects (Nematbakhsh et al., 2017). Therefore, the side effects of this medication need to be assessed in different categories of ages for both sexes, and clinical trials studies for this subject are suggested.

Conflict of interest
The authors have declared that no conflict of interest exists.

Acknowledgments
This research was supported by Isfahan University of Medical Sciences (Grant # 249250).

References
Ahmed SB, Fisher NDL, Hollenberg NK (2007). Gender and the renal nitric oxide synthase system in healthy humans. Clin J Am Soc Nephrol, 2, 916–31.
Aydin I, Agilli M, Aydin FN (2014). Gender differences influence renal injury in cisplatin- treated rats: biochemical evaluation. Biol Trace Elem Res, 158, 275.
Daniel G, Hahn K, Bravo L, et al (1997). The effect of a single therapeutic dose of cisplatin on GFR in dogs. Oncol Rep, 4, 153-6.
El-Arabey AA (2015). Gender difference in cisplatin-induced nephrotoxicity in a rat model. Nephrourol Mon, 7, e23595.
Eshraghi-Jazi F, Nematbakhsh M, Nasri H, et al (2011). The protective role of endogenous nitric oxide donor (L-arginine) in cisplatin-induced nephrotoxicity: Gender related differences in rat model. J Res Med Sci, 16, 1389-96.
Ghasemi M, Nematbakhsh M, Pezeshki Z, et al (2016). Nephroprotective effect of estrogen and progesterone combination on cisplatin- induced nephrotoxicity in ovariecortized female rats. Indian J Nephrol, 26, 167-75.
Ghayyoomi M, Soltani N, Nematbakhsh M, et al (2015). The effect of an specific inducible NO synthase inhibitor, S-methylisothiourea hemisulfate on cisplatin-induced nephrotoxicity; gender-related differences. Adv Biomed Res, 4, 130.
Haghighi M, Nematbakhsh M, Talebi A, et al (2012). The role of angiotensin II receptor 1 (AT1) blockade in cisplatin-induced nephrotoxicity in rats: gender-related differences. Ren Fail, 34, 1046-51.
Lu Y, Kawashima A, Horii I, et al (2005). Cisplatin-induced cytotoxicity in BSO-exposed renal proximal tubular epithelial cells: sex, age, and species. Ren Fail, 27, 629-33.
Naseem I, Hassan I, Alhaza IM, et al (2015). Protective effect of riboflavin on cisplatin induced toxicities: a gender-dependent study. J Trace Elem Med Biol, 29, 303-14.
Nasri H (2013). Cisplatin therapy and the problem of gender-related nephrotoxicity. J Nephropharmacol, 2, 13-4.
Nematbakhsh M, Ebrahimian S, Toosyerkani M, et al (2013a). Gender difference in Cisplatin-induced nephrotoxicity in a rat model: greater intensity of damage in male than female. Nephrourol Mon, 5, 818-21.
Nematbakhsh M, Pezeshki Z (2013b). Sex-related difference in nitric oxide metabolites levels after nephroprotectant supplementation administration against cisplatin-induced nephrotoxicity in Wistar rat model: The role of vitamin E, erythropoietin, or n-acetylcysteine. ISRN Nephrol, 2013, e612675.
Watanabe T, Akishita M, Toba K, et al (2000). Influence of sex and age on serum nitrite/nitrate concentration in healthy subjects. Clin Chim Acta, 301, 169–79.
Winston JA, Safirstein R (1985). Reduced renal blood flow in early cisplatin-induced acute renal failure in the rat. J Am Physiol, 249, 490–6.
Zamani Z, Nematbakhsh M, Eshraghi-Jazi F (2016). Effect of enalapril in cisplatin-induced nephrotoxicity in rats; gender-related difference. Adv Biomed Res, 5, 14.