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ORIGINAL ARTICLE

All-trans retinoic acid prevents cisplatin-induced nephrotoxicity in rats

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Abstract

The aim of this study is to investigate the effects of all-trans retinoic acid (ATRA) use on cisplatin (CP)-induced nephrotoxicty. Twenty-eight rats were randomly divided into four groups. The rats in the control group were injected a single dose of 1 ml/kg saline intra-peritoneally (IP) during 10 days. The rats in the ATRA group were injected a single dose of ATRA during 10 days. The rats in the ATRA+CP group were injected a single dose of CP on the fourth day of the 10 days of ATRA treatment. The rats in the CP group were injected a single dose of CP on the fourth day of 10 days without administering a treatment. After treatment, the groups were compared with regard to total antioxidant status (TAS), total oxidant status (TOS), and oxidative stress index (OSI) levels in renal tissue and renal histopathology. The serum creatinine and urea values were statistically significantly higher in the CP group compared to the other groups. The serum creatinine and urea values were statistically significantly lower in the ATRA+CP group when compared to the CP group. Although the TOS and OSI levels were found to be lower in the ATRA+CP group compared to the CP group, the difference was not statistically significant. Administration of ATRA together with CP was observed to reduce the histopathologic destruction in the kidney and lead to mild tubular degeneration, vacuolization, and necrosis (57.1% grade 1; 28.6% grade2, and 14.3% grade 3 necrosis). The results of the present study have revealed that ATRA administration ameliorates CP-induced nephrotoxicity; however, further studies are required to identify this issue before clinical application.

Keywords Nephrotoxicity · All-trans retinoic acid · Cisplatin

Introduction

Cisplatin (CP) is an alkylating antineoplastic agent used for treatment of many solid organ cancers (Ezaki et al. 2017). Although the use of less toxic and more biological molecules has been investigated in the treatment of cancer, today, cisplatin still maintains its importance in the treatment of urological malignancies. CP is used particularly for treatment of testicular and urinary bladder cancer in the urology discipline. The side effects restrict its use despite being an effective antineoplastic agent. Nephrotoxicity is a significant side effect of CP. Cell death occurring due to exposure of renal tubular cells to high concentrations of toxic substances negatively affects the absorption and secretion functions of the kidney. (Nematbakhsh et al. 2012). The cellular mechanism of CP-induced nephrotoxicity is not clear yet. Free radicals and reactive oxygen species (ROS)-related renal tissue injury have been accounted for the molecular mechanism of CP-induced nephrotoxicity in many studies (Saifi et al. 2018). ROS are usually formed during drug metabolism and lead to apoptosis through causing destructive effects, such as lipid peroxidation, enzyme inactivation, and oxidative damage (Gómez-Sierra et al. 2018). Therefore, experimental animal studies have been performed with many antioxidant molecules in order to detect the useful molecule for prevention of CP-induced nephrotoxicity (Alibakhshi et al. 2018; Jung et al. 2017; Crona et al. 2017).

Retinoids have functions such as vision, growth, reproduction, epithelial cell endurance, glycoprotein synthesis, anticancer, and antioxidant effects in the body (Elsayed et al. 2016). 9-cis retinoic acid and all-trans retinoic acid (ATRA), which are the biological active metabolites of vitamin A, are produced via

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alcohol dehydrogenases and tissue-specific aldehyde dehydrogenases (Elsayed et al. 2016; Penniston and Tanumihardjo 2006). ATRA is the most available retinoid form in nature. ATRA may catch free radicals without interacting with biological targets, may prevent free radical formation through chain-breaking effects and may show antioxidant effect through hindering lipid peroxidation in the cellular membrane (Oseto et al. 2003). ATRA was also shown to have antiproliferative, anti-inflammatory, and anticancer effects (Gudas 2012).

Although the concurrent use of ATRA and CP was reported to have a synergistic effect for treatment of cancer cells, the number of studies on this subject investigating the influences of ATRA administration on CP-induced nephrotoxicity is insufficient (Moreb et al. 2017; Tang and Gudas 2011). The aim of the present study was to investigate the influences of ATRA administration on CP-induced nephrotoxicity in an experimental animal model.

Materials and methods

Animal model

Twenty-eight Wistar albino rats were purchased from the animal laboratory of Dokuz Eylul University. The animals were kept in quarantine for 7 days before the study. The rats were kept in a room at 23–24 °C temperature and 50–55% humidity. They were kept in clean 40 × 60 cm standard plastic cages with water and food ad libitum, 12-h dark and 12-h light period. The animals were fed with 8 mm of pellet food and daily fresh tap water. All animal procedures were conducted in accordance with The Guide for The Care and Use of Laboratory Animals of the Research Council after approval from the local ethics committee of animal tests had been obtained from the Dokuz Eylul University. Cisplatin was purchased from Kocak Pharma, Istanbul, Turkey, and ATRA was purchased from Roche, Istanbul, Turkey.

Twenty-eight rats were randomly divided to four groups. The rats in the control group were injected a single dose of 1 ml/kg saline intraperitoneally (IP) during 10 days. Saline was applied to the control group because it is an inert molecule. The rats in the ATRA group were injected a single dose of (7.5 mg/kg IP) ATRA for 10 days. The aim for formation of the ATRA-given group without platinum was to evaluate the oxidant and antioxidant capacity of ATRA itself. The rats in the ATRA+CP group were injected a single dose of CP (7 mg/kg IP) on the fourth day of 10-day ATRA treatment (7.5 mg/kg IP). The rats in the CP group were injected a single dose of CP (7 mg/kg IP) on the fourth day of 10 days without administering a treatment. The dose and duration of drug administration were determined based on similar studies in the literature (Elsayed et al. 2016; Ewees et al. 2015; Aburto et al. 2014).

All animals were sacrificed with high dose ether on the 11th day after completing 10 days of the study period. Creatinine measurement was carried out once and blood sample was obtained on the 11th day of the study by cardiac puncture. The abdomen was opened with a midline incision and bilateral nephrectomy was performed immediately. The kidney that would undergo biochemical analysis was washed with cold saline twice and stored at − 80 °C until the day of the analysis. The other kidney was placed in formol solution and stored for histopathology analysis.

Biochemical analysis

Renal tissues were tenfold diluted with 50 mM phosphate buffer saline (PBS) and homogenized with mechanic homogenizer (TissueLyser LT, Qiagen, Dublin, Ireland). The homogenate was centrifuged at 10,000 rpm for 15 min at 4 °C. The total antioxidant status (TAS) and total oxidant status (TOS) levels in renal tissue were measured in the autoanalyzer (AU5800, Beckman Coulter Inc., CA, USA) using the Rel Assay brand of commercial kits (Rel Assay Diagnostics, Gaziantep, Turkey) as defined by Erel et al. (2004, 2005). The water-soluble analogue of vitamin E, Trolox, was used as calibrator for TAS, and the results were expressed as μmol H2O2 equivalent/g. Hydrogen peroxide was used as calibrator for TOS, and the results were expressed as μmol H2O2 equivalent/g. Oxidative stress index (OSI) is defined as the TOS/TAS ratio. OSI was calculated using the following formula: OSI = [(TOS, μmol H2O2 equiv./g)/(TAS, μmol Trolox equiv./g) × 100] (Erel 2005). The results were expressed as arbitrary unit (AU).

Histopathological examination

The renal tissues were embedded into paraffin blocks following tissue follow-up procedure after having been fixed in 10% formalin solution and 4 μm of sections were obtained, stained with hematoxylin-eosin, and examined under × 200 microscope (Olympus CX31, Tokyo, Japan). The changes in tubular epithelium such as tubular vacuolization, degeneration, cell desquamation, and necrosis were examined in detail. At least 50 proximal tubules and glomeruli were examined. Renal tissue was examined semiquantitatively in accordance with the previous studies in the literature and the degree of tubular change was scored. The lesion severity was scored between 0 and 4 as follows: 0: normal, 1: < 25% injury in tubular epithelium (mild), 2: 25–50% injury in tubular epithelium (moderate), 3: 50–75% injury in tubular epithelium (severe), 4: complete necrosis (very severe) (Ilbey et al. 2009).

Statistical analysis

Categorical variables were expressed as numbers (*n*) and percentages (%), and the numerical variables were expressed as mean and standard deviation if they met the parametric test

assumptions, and as median (minimum-maximum) if they did not meet the parametric test assumptions. The normality distribution of the numerical variables was tested with the Shapiro-Wilk test. The intergroup differences were evaluated with the one-way variance analysis and the Tukey test as post hoc test if they met the parametric test assumptions, and the Kruskal-Wallis test and the Dunn-Bonferroni test as the post hoc test if they did not meet the parametric test assumptions.

The correlation between the categorical variables in the group was tested with the Fisher-Freeman-Halton exact test. The data analysis was performed using the Statistical Package for the Social Science (SPSS Inc., Chicago, Illinois, USA) version 22.0, and a p value of < 0.05 was considered significant.

Results

The finding of cisplatin-induced significant external toxicity or rat death was not observed during the trial. Serum creatinine and urea values were statistically significantly higher in the CP group compared to the other groups. Serum creatinine and urea values were statistically significantly lower in the ATRA+CP group when compared to the CP group only. The TOS and OSI levels were statistically significantly higher in the CP group compared to the control and the ATRA groups. Although the TOS and OSI levels were found lower in the ATRA+CP group compared to the CP group, the difference was not statistically significant. No significant difference was observed between the groups with regard to the TAS levels. Box plots, which represent the creatinine and biochemistry findings of the groups, have been presented in Fig. 1. Renal parenchyma and glomerular structure were found to be normal in the control and the ATRA groups (Fig. 2a). Mild tubular degeneration, vacuolization, and necrosis were observed in the ATRA+CP group (Fig. 2b). Severe histopathological damage was observed in rats undergoing administration of CP. In this group, light microscopy revealed severe necrosis and cystic dilation in the renal tubule (Fig. 2c). Comparison of the groups with regard to biochemical and histopathologic findings has been presented in Table 1.

Discussion

The present study has revealed that CP-induced nephrotoxicity can be reduced with ATRA administration, which is an anti-inflammatory and antioxidant molecule. When compared with other organs, some biochemical and physiological features of the kidney make it more susceptible to ischemic and toxic injury. High concentration of toxic molecule extraction from renal tissue may lead to renal damage. Cisplatin is an effective chemotherapeutic agent, which is widely used in the treatment

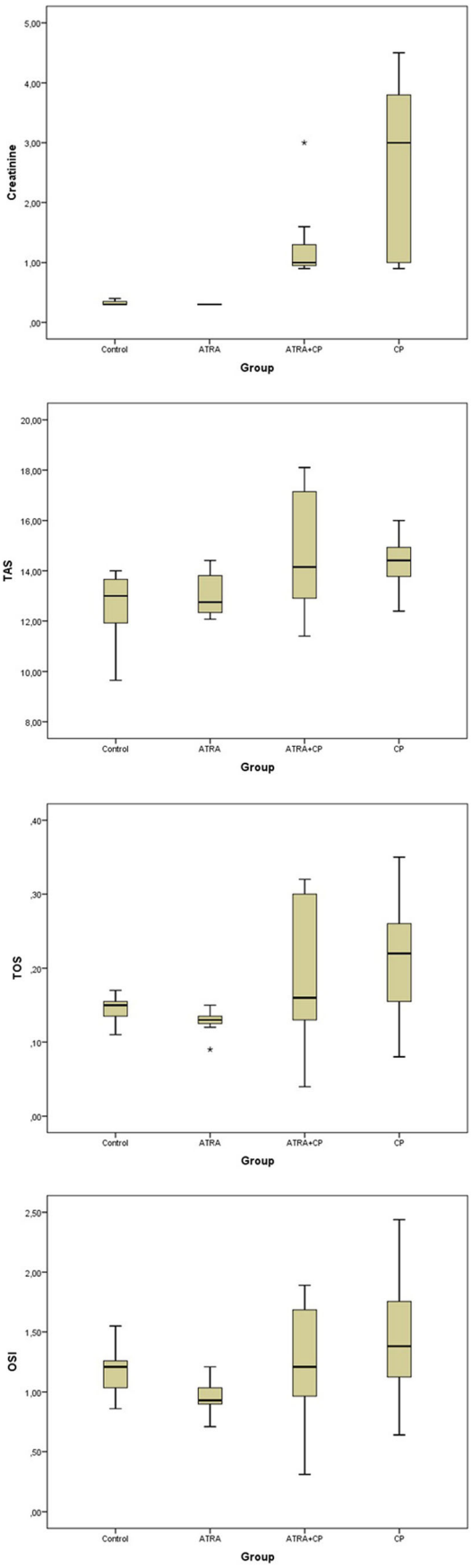

Fig. 1 Comparison of biochemical findings among groups

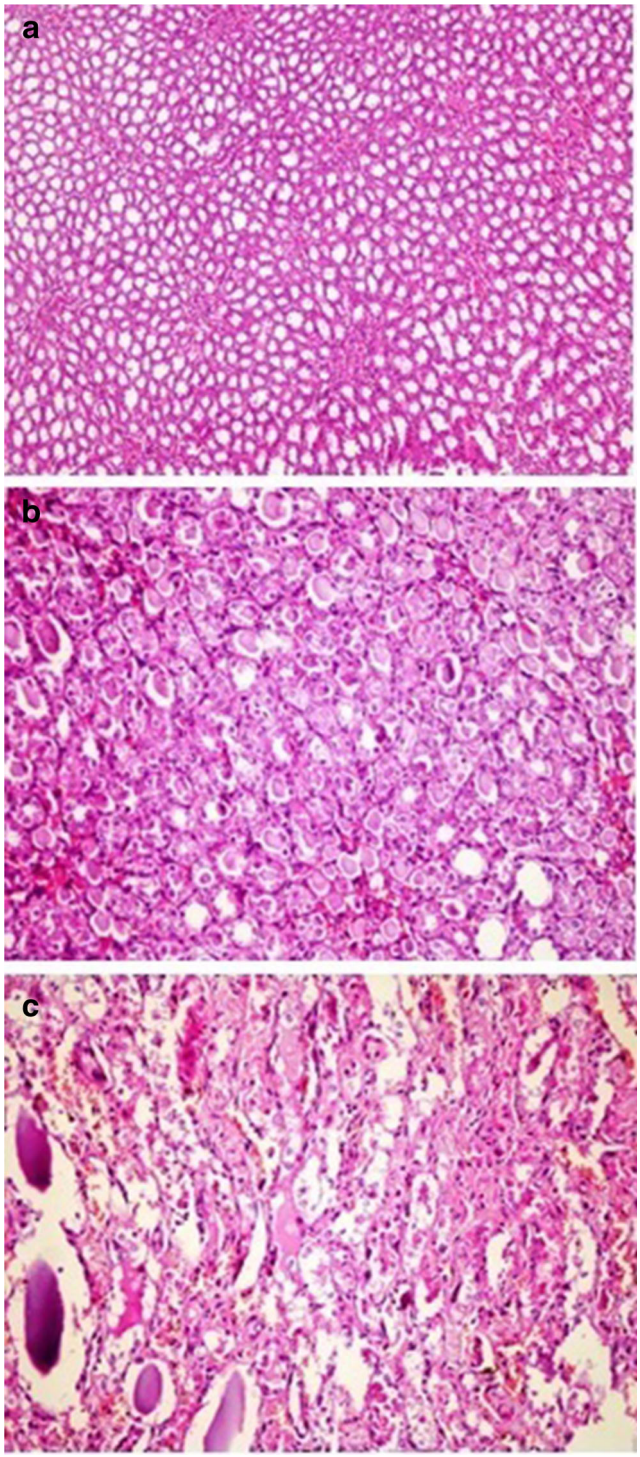

Fig. 2 Kidney morphololology in **a** control group, **b** ATRA+CP group, **c** CP group

of many solid organ tumors. Nephrotoxicity is the most important side effect of CP, which restricts the use of the drug (Kim et al. 2015). The only molecule that is approved by the Food and Drug Administration (FDA) for prevention of this toxic effect is amifostine, which is used in treatment of ovarian cancer. Amifostine shows a scavenger effect through binding to free radicals that are produced by CP (Bouhadjari et al. 2016). In the literature, experimental studies have been conducted with many antioxidant molecules for prevention of CP-induced nephrotoxicity (Alibakhshi et al. 2018; Jung et al. 2017).

Consistent with the literature, the serum urea and creatinine levels were found to be statistically significantly elevated in the CP group compared to the control group. This elevation indicates CP-induced acute renal damage. ATRA+CP administration was found to have positive effects on preservation of renal functions through leading to significant reduction in urea and creatinine levels compared to the CP group.

The cellular mechanism of CP-induced nephrotoxicity is still not entirely clear. ROS-producing pro-oxidants and ROS-scavenger antioxidant molecules are in balance in normal cells. CP was shown to lead to toxic effects through leading to free radical and ROS production in renal tissue in many studies in the literature (Cekmen et al. 2009; Ozbek et al. 2010). Cellular damage, which develops due to toxic substances such as CP leads to impairment of this balance toward the oxidative side. Several studies have shown that formation of lipid peroxidation in the nephron cell membrane due to ROS production by CP administration is associated with CP-induced nephrotoxicity. In vivo studies have shown that CP increases the apoptosis, and as a result induces the inflammation and fibrogenesis (Oseto et al. 2003). ATRA is known to have a free radical scavenger effect. In our study, the TOS and OSI levels, which indicate oxidative stress, were found to be statistically significantly higher in the CP group compared to the control group. ATRA administration together with CP was observed to lead to a reduction in TOS and OSI levels. The reduction in oxidative stress not being statistically significant may be related to the insufficient dose of ATRA. Not observing a significant difference between the groups with regard to TAS levels, which is the indicator of antioxidant activity, may result from elevated antioxidant molecules in renal tissues for balancing the increased oxidative stress due to CP administration.

It was shown that renal aplasia, ureter anomalies, and horse shoe kidney could develop during fetal development in rats with severe vitamin A deficiency (Lelievre-Pegorier et al. 1998). On the contrary, there are studies showing that high dose vitamin A could lead to renal damage (Kavukcu et al. 2001). Kim et al. (2015) reported that 10 mg/kg ATRA administered per orally for 16 weeks reduced diabetic nephropathy. Similarly, Han et al. (2004) reported that ATRA treatment had renoprotective effects through reducing the inflammatory process in rats developing diabetic nephropathy. Moulder et al. (2002) observed that ATRA administration accelerated the radiation-induced nephropathy in rats. In the abovementioned studies, ATRA seems to be protective against diabetic nephropathy and increases radiation-induced nephrotoxicity, and this may be related to the difference in the mechanisms of formation of diabetic nephropathy and

Table 1 Biochemical and histopathological findings in the experimental groups

Variables	Control	ATRA	ATRA+CP	CP
Creatinine (mg/dL) Median (min-max)	0.3 (0.3–0.4)	0.3 (0.3–0.3)	1 (0.9–3)[a,b]	3 (0.9–4.5)[a,b,c]
Urea (mg/dL) Median (min-max)	49 (36–51)	47 (41–50)	22 (21–520)[a,b]	508 (19–659)[a,b,c]
TAS (μmol Trolox equiv./L) Median (min-max)	13 (9.6–14)	12.7 (12–14.4)	14.2 (11.4–18.1)	14.4 (12.4–16)
TOS (μmol H2O2 equiv./L) Mean ± SD	0.144 ± 0.215	0.127 ± 0.189	0.197 ± 0.109[a,b]	0.211 ± 0.091[a,b]
OSI mean ± SD	1.173 ± 0.223	0.96 ± 0.157	1.244 ± 0.557[a,b]	1.46 ± 0.601[a,b]
Grade of necrosis				
Grade 0 (normal)	7 (100%)	6 (85.7%)	0	0
Grade 1 (< 25% injury in tubular epithelium) (mild)	0	1 (14.3)	4 (57.1%)	0
Grade 2 (25–50% injury in tubular epithelium) (moderate)	0	0	2 (28.6%)	3 (42.9%)
Grade 3 (50–75% injury in tubular epithelium) (severe)	0	0	1 (14.3%)	2 (28.6%)
Grade 4 (complete necrosis) (very severe)	0	0	0	2 (28.6%)

[a] $p < 0.05$ compared with control group

[b] $p < 0.05$ compared with ATRA group

[c] $p < 0.05$ compared with ATRA+CP group

radiation-induced nephrotoxicity. In diabetes, which is a chronic process, the sensitivity of retinoic acid receptors to the ATRA molecule may be different to radiation-induced toxicity. In the literature, only one study is available investigating the effects of ATRA treatment on CP-induced nephrotoxicity conducted by Elsayed et al. (2016). The authors reported that 7.5 mg/kg/day ATRA administered via the IP route for 10 consecutive days potentiated CP-induced nephrotoxicity. On the contrary to that study, ATRA was found to ameliorate CP-induced nephrotoxicity despite the fact that it was administered at the same dose and same duration in our study. This difference may be related to the different sensitivities of rats to ATRA due to the utilization of different rat types in two studies. Further studies are needed to better understand this issue.

Consistent with the literature, CP administration was observed to lead to characteristic histopathologic changes in the renal structure. While CP administration may affect different regions in the kidney, the most evident histopathologic change is acute tubular necrosis in CP-induced nephrotoxicity (Arany and Safirstein 2003). In particular, distal and collecting tubules are affected. In many studies, oxidative molecules were accused for CP-induced histopathologic damage (Alibakhshi et al. 2018; Jung et al. 2017; Cekmen et al. 2009). The inflammatory response, which develops against these molecules, contributes to histopathologic damage. In our study, ATRA administration together with CP was observed to reduce renal destruction and lead to mid tubular degeneration, vacuolization, and necrosis. We consider that this improvement results from the anti-inflammatory and antioxidant effects of ATRA.

The model used in our study may pioneer further rat studies due to it being easy to apply, using TAS and TOS instead of analyzing many oxidant and antioxidant molecules separately, and being more economic. The issue investigated in this study may be investigated in more detail through administering different ATRA doses or creating an experimental tumor model. Further experimental animal studies should be conducted to investigate the pathway of reducing the CP-induced nephrotoxicity by ATRA administration. A limitation of this study is that it did not support the results of the study with immune histochemical and electromicroscopic findings.

Conclusions

The present study has confirmed that CP treatment has destructive effects on renal tissue. The results of the study have revealed that ATRA administration ameliorates CP-induced nephrotoxicity. These beneficial effects of ATRA administration may be related to its antioxidant and anti-inflammatory effects. We consider that further studies are required before clinical use of ATRA for preserving renal histopathology and functions in patients receiving CP treatment.

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Author contributions CY and EEY conceived and designed research. CY, FDA, and SE conducted experiments. EK, VU, and MU contributed new reagents or analytical tools. CY and OC analyzed data. YOI, BB, and

ZK made supervision. CY wrote the manuscript. All authors read and approved the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval All procedures were performed in accordance with the Guide for the Care and Use of Laboratory Animals of the Research Council after approval had been obtained from the Dokuz Eylül University local ethical committee of animal experiments.

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