Original Article

The Prevention of Cisplatin-Induced Nephrotoxicity: A General Consensus Statement of a Group of Oncologist-Hematologists, Adult and Pediatric Nephrologists, Radiation Oncologists, Clinical Pathologists, Clinical Pharmacologists, and Renal Physiologists on Cisplatin Therapy in Cancer Patients

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Abstract

Backgrounds: Most of the cancer patients with solid tumor are subjected to chemotherapy with cisplatin (CP) in clinic. However, the most side effect of CP is nephrotoxicity, which limits the treatment. The aim of study was to develop a general consensus statement for CP therapy in clinic to limit the drug-induced nephrotoxicity. **Methods:** A total of 30 oncologist-hematologists, adult and pediatric nephrologists, radiation oncologists, clinical pathologist clinical pharmacologist, and renal physiologist participated in a workshop, and in order to reduce the incidence of CP-induced nephrotoxicity, a general consensus was developed. **Results:** The developed general consensus was focused on some items such as age, sex, female hormone, nonsteroidal anti-inflammatory drugs (NSAID), renin–angiotensin system inhibitor drugs, glomerular filtration rate, hydration methods, contrasts, antioxidants, dextrose, and magnesium. **Conclusion:** The agreement between participants for CP therapy in clinic was achieved, and this general consensus was announced to be implemented in the hospitals.

Keywords: *Cisplatin, consensus, nephron, toxicity*

Introduction

Cisplatin (CP) is the most frequently used drug for cancer treatment. Acute kidney injury, glomerular capillary endothelial injury, tubulointrestitial disease, and renal electrolyte disorders are the most frequent adverse effects of CP therapy, which are major causes of morbidity and mortality among cancer patients. Volume depletion, preexisting kidney disease, cardiovascular disease, diabetes, and concurrent use of nonsteroidal other nephrotoxic drugs such as nonsteroidal anti-inflammatory drugs (NSAID) are the major risk factors for CP-induced nephrotoxicity.

There are some risk factors associated with the incidence of CP-induced nephrotoxicity.[1] In addition, many other clinical and experimental studies have explained the CP-induced nephrotoxicity risk factors, including age,[2-4] gender,[5-7] low glomerular filtration rate (GFR),[8] sex hormone estrogen,[9] dehydration,[8] hydration process during CP therapy with dextrose,[10] NSAID, and contrast media.[11] Special attentions also were made to antioxidant therapy to attenuate CP-induced nephrotoxicity in the laboratory.[12-16] Based on new findings, the general consensus will be helpful to prevent nephrotoxicity during CP therapy.

Methods

A total of 30 oncologist-hematologists, adult and pediatrics' nephrologists, radiation oncologists, clinical pathologists, clinical pharmacologist, and renal physiologists participated in a workshop to develop a general consensus to reduce the incidence of CP-induced nephrotoxicity in Isfahan, Iran hospitals. The announcement for the workshop was performed 2 months earlier, and the participants were asked to review the related materials in the literature including their experiences to obtain the general consensus questions. Based on the suggestions, four main subjects related to

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Table 1: A general consensus statement on cisplatin therapy in cancer patients: the associated items and factors and principals

General consensus parts	Items	Principals and descriptions
Part one: General consideration factors	Age and gender	Principal 1: CP-induced nephrotoxicity is age and gender related.[2-8,22] The age >60 years has more risk for CP-induced nephrotoxicity
	RAS inhibitor drugs	Principal 2: The drugs like losartan and enalapril may increase the risk of CP-induced nephrotoxicity in female gender[5,23,24] due to expression difference of RAS receptors between female and male
	Female sex hormone estrogen	Principal 3: Based on some laboratory studies, high levels of estrogen along with CP may increase the risk of CP-induced nephrotoxicity[9,25-28]
	eGFR	Principal 4: Determining the eGFR before treatment with the CP is necessary and important[29,30]
Part two: Prohibition items	GFR >50 ml/min per 1.73 m^2 body surface	Principal 5: Although when eGFR is less than 60 ml/min/1.73 m^2 body surface,[8] it is not recommended for CP treatment; however, based on other finding[29] and our clinical experience, CP treatment is advised when the eGFR is greater than 50 ml/min/1.73 m^2 body surfaces. It is important that when GFR is less than 50 ml/min per 1.73 m^2 body surface, the administration of CP can be made only with the approval of a multidisciplinary consulting medical team
	Hydration with dextrose	Principal 6: Hydration with dextrose (dextrose diuresis) does not attenuate CP-induced nephrotoxicity and should be avoided because dextrose may increase the risk of CP-induced nephrotoxicity.[10,31] Before and after administration of CP, hydration should be performed with normal saline plus potassium chloride (KCl)
	Mannitol	Principal 7: There is controversy regarding the use of mannitol for diuresis. On the basis of many agreed and opposed studies related to hydration with mannitol,[17-21,32,33] special care is needed when mannitol administration is applied by a multidisciplinary consulting medical team
	NSID*	Principal 8: There is interaction between NSID and CP; therefore, using NSID with CP increases the risk of CP-induced nephrotoxicity and must be avoided[4,11]
	Contrast media*	Principal 9: Co-administration of nephrotoxic drug such as CP with contrast media is a high-risk factor to develop CP-induced nephrotoxicity[4,11]
	Antioxidant supplements*	Principal 10: There are a lot of basic researches and less clinical research about the use of antioxidants to reduce CP-induced nephrotoxicity.[12-14, 34-36] However, prescription of herbal or synthetic antioxidants supplements to reduce CP-induced nephrotoxicity without clinical scientific citation or the approval of a multidisciplinary consulting medical team is not recommended
Part three: requirements and permissions items	Suitable hydration agents	Principal 11: Before and after administration of CP, hydration should be performed with normal saline (1 l/2-4 h) plus KCl
	Magnesium administration	Principal 12: There are numerous basic and clinical studies that make it doubtful about the role of magnesium in prevention of CP-induced nephrotoxicity;[37-45] therefore, administration of intravenous magnesium with hydration is recommended only if serum level of magnesium is lower than normal
Part four: Others	Diabetes, acidosis, hypokalemia, uricosuric, hyperuricemia, infection, etc.	Principal 13: There are many other pathological conditions such as diabetes, kidney transplantation, acidosis, hypokalemia, hyperuricemia, antibiotics, infection, etc. that need to be considered on a case-by-case basis

*Nephrotoxic antibiotic such as aminoglycoside, vancomycin, and amphotericin B that are commonly used to treat infections in patients with cancer. RAS: Renin-angiotensin system; eGFR: Estimated GFR; NSID: Nonsteroidal anti-inflammatory drugs; KCI: Potassium chloride

CP therapy were assigned for the workshop discussion as followings:

(1) Based on the clinical evidences, to reduce the CP-induced nephrotoxicity, the CP prescribing should be accompanied by hydration of the patient. Therefore, the agreement on the hydration process seems necessary.
(2) Based on the experimental evidences, some synthetic and herbal antioxidant supplements can reduce CP-induced nephrotoxicity, and it seems necessary to agree on this issue in the process of CP therapy.
(3) From the clinical point of view, the patients should have favorable clinical conditions for receiving CP (e.g., the minimum level of GFR) and therefore agreeing to these issues in the CP prescribing process seems essential.
(4) Some drugs along with CP increases the risk of nephrotoxicity and it is therefore necessary to agree on these issues in the process of CP prescribing.

The subjects with the 16 questions were submitted to the participants before the workshop day. On the day of workshop, two nephrologists and two oncologist-hematologists also were asked to summarize the literature reviewing results. During the discussion, some other questions also were created by the participants.

Therefore, all questions, one by one, were subjected to panel discussion, and based on the opinion of all, the agreement was created. Finally, three workshop members were assigned to prepare the draft of general consensus, and then the draft was finalized. This general consensus included 13 principals or important items that must be considered during CP therapy to limit CP-induced nephrotoxicity.

Results

The general consensus included four different parts.

Part one: general consideration factors include 4 items (principals 1–4)

The general consideration factors were listed in Table 1. Age, gender, concurrent use of renin–angiotensin system inhibitor drugs, the level of female sex hormone estrogen, and estimated GFR should be considered in the first step.

Part two: prohibition items include 6 items (principals 5–10)

To avoid CP-induced nephrotoxicity, some items are forbidden during CP therapy, including GFR <50 ml/min/1.73 m^2 body surface, hydration with dextrose, NSAID prescribing, given contrast media during 2 weeks post-CP administration, and prescribing antioxidant without enough clinical evidences [Table 1]. Due to existence of positive and negative results for mannitol prescribing,[17-21] special care is recommended when mannitol administration is applied.

Part three: requirement and permission items include 2 items (principals 11–12)

There are two major requirements and a major license. Before and after administration of CP, hydration should be performed with normal saline plus potassium chloride (KCl). Administration of intravenous magnesium with hydration is recommended only when the serum level of magnesium is lower than normal [Table 1].

Part four: Others include 1 item (principal 13)

There are many other pathological conditions such as diabetes, kidney transplantation, acidosis, hypokalemia, hyperuricemia infection, etc. that need to be considered on a case-by-case basis.

Conclusion

We suggested several new points that need to be considered during CP administration. Female sex hormone estrogen,[9,25-28] hydration with dextrose,[10,31] and concurrent use of renin–angiotensin system inhibitor drugs[5,23,24] are the subjects that included in this general consensus. In order to obtain a more complete general consensus or guideline for CP therapy, more clinical trial researches are needed.

Author contribution

All the authors (FA, MM, and MN) were contributed to design the workshop, to search the main literature review, to manage the workshop, and to wright the article draft. The article was finalized by MN.

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Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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Conflicts of interest

There are no conflicts of interest.

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