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NEPHROLOGY - ORIGINAL PAPER

# Evaluation of the protective effect of Cystone® against cisplatin-induced nephrotoxicity in cancer patients, and its influence on cisplatin antitumor activity

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**Abstract**
*Purpose* Evaluating the role of cystone, a polyherbal preparation, in protecting cancer patients against cisplatin-induced nephrotoxicity, and its impact on the cytotoxic activity of cisplatin.
*Methods* A prospective open-label randomized controlled trial conducted on 49 cancer patients who received six cycles of 70 mg/m$^2$ cisplatin-based regimens. The study comprised two groups, a control group (A) in which 28 patients received cisplatin without cystone supplement, and an experimental group (B) in which 21 patients received cisplatin with cystone supplement. Renal function parameters including serum creatinine, creatinine clearance, blood urea, and serum cystatin C were compared between both groups throughout chemotherapy cycles. Patient response to treatment was evaluated in both groups after 3rd and 6th cycles.
*Results* At the end of the study, mean levels of serum creatinine, blood urea, and serum cystatin C were significantly lower, whereas creatinine clearance was significantly higher in group (B) compared with group (A). In group (B), there was no significant difference between mean levels of renal markers at baseline and after completion of treatment; while significant changes were observed in group (A). Grading of acute kidney injury according to Common Terminology Criteria for Adverse Events revealed significantly better renal status among patients in group (B) "grades 0 and 1 in 76 and 24 % of the patients, respectively" compared with group (A) "grades 0, 1, and 2 in 36, 32, and 32 % of the patients, respectively". Based on Response Evaluation Criteria in Solid Tumors, there was no significant difference between both groups.
*Conclusions* Cystone can protect cancer patients from cisplatin nephrotoxicity without interfering with its antitumor activity.

**Keywords** Cisplatin · Cystone · Nephrotoxicity · Serum creatinine · Creatinine clearance · Blood urea · Serum cystatin C

## Introduction

Cisplatin is an alkylating-like agent that is widely used to treat a variety of malignancies [1]. Beside its important antitumor properties, cisplatin presents several toxic effects. Its toxicity profile includes nausea, vomiting, neuropathy, ototoxic effects, and myelosuppression. However, the major dose-limiting adverse effect appears to be renal toxicity [2, 3]. Renal insufficiency begins several days after cisplatin administration, as revealed by a decrease in glomerular filtration rate, increased blood urea nitrogen and serum creatinine concentrations. Depending on the dose and cumulative effect, cisplatin nephrotoxicity can lead to acute renal failure [4].

The early intervention developed to overcome such toxicity was hydration. With no consensus on a standard hydration method, several hydration protocols varying in

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quantity and duration have been proposed. Unfortunately, renal toxicity is reduced but not completely prevented by hydration [5]. Various approaches have been attempted to reduce the incidence of cisplatin-induced renal impairment. For years, several agents have been tested for preventing such detrimental effect [6].

Cystone (manufactured by The Himalaya Drug Company, Bangalore, India) is a polyherbal preparation based on ancient ayurvedic system of medicine. The plants used in the preparation are well known for their beneficial actions on the kidney (Table 1). Cystone has been used for many years in the treatment for various urinary tract complications such as urolithiasis, burning micturition, neuro-ureterolithiasis, urinary tract complications in pregnancy and other renal disorders [7]. Several studies have tested and showed the capability of either cystone, as a whole preparation [8, 9], or its herbal components [10, 11] to prevent cisplatin-induced nephrotoxicity in laboratory animals. The current study is considered the first study to investigate the nephroprotective effect of cystone clinically in cisplatin-treated cancer patients, and whether or not it has an influence on the efficacy of the treatment.

## Patients and methods

### Patients

This was a prospective open-label randomized controlled trial which included 49 cancer patients who received six cycles of cisplatin-based chemotherapy (70 mg/m$^2$/cycle) at Clinical Oncology Department, Tanta University Hospital, Tanta, Egypt. The study was conducted during the period from February 2011 to December 2012 after ethical approval was granted from the Faculty of Medicine Ethics Committee, Tanta University (Approval code: 341/12/10), and a written informed consent was obtained from each participant. Inclusion criteria were: patient age $\geq$18 years, Eastern Cooperative Oncology Group (ECOG) scale performance status (PS) $\leq$2, adequate hematological, renal and hepatic functions and no comorbidity (such as diabetes or hypertension) or coadministration of any nephrotoxic drug or a history of cisplatin administration.

### Treatment

Patients received cisplatin-based chemotherapy (cisplatin dose: 70 mg/m$^2$) once every 21 days. A predefined I.V hydration regimen was applied for all patients (Table 2).

Patients were randomly assigned to the control group (A) or experimental group (B). In group (A), 28 patients received cisplatin without cystone supplement or any additional preparation (i.e., no placebo); while 21 patients in group (B) received cisplatin with cystone supplement. Cystone was given in a dose of two tablets thrice daily for the entire period of the study from the beginning of treatment at the 1st cycle till the 21st day after chemotherapy administration in the 6th cycle.

### Evaluation of renal function and patient response to cisplatin-based treatment

Serum creatinine (S. Cr.), creatinine clearance (Cr. Cl.), and blood urea were measured for all patients before starting the treatment as a baseline and at the end of each chemotherapy cycle (21 days after chemotherapy administration in each cycle). Serum cystatin C was evaluated in all patients before starting the treatment as a baseline, at the end of the 3rd cycle, and at the end of the 6th cycle. Creatinine clearance was estimated via Cockcroft–Gault method [5, 12, 13] and its values were adjusted for the body surface area (BSA) of 1.73 m$^2$ to allow comparison of results. Nephrotoxicity was evaluated in accordance with Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 for Acute Kidney Injury (AKI). Assessment of response to treatment was done at the end of

**Table 1** Composition of cystone tablet

| | Plant name | Family | Quantity (mg) |
|---|---|---|---|
| Extracts | Shilapuspha (*Didymocarpus pedicellata*) | Gesneriaceae | 65 |
| | Pasanabheda (*Saxifraga ligulata*) | Saxifragaceae | 49 |
| | Manjishtha (*Rubia cordifolia*) | Rubiaceae | 16 |
| | Nagaramusta (*Cyperus scariosus*) | Cyperaceae | 16 |
| | Apamarga (*Achyranthes aspera*) | Amaranthaceae | 16 |
| | Gojiha (*Onosma bracteatum*) | Boraginaceae | 16 |
| | Sahadevi (*Vernonia cinerea*) | Compositae | 16 |
| Powders | Shilajeet (purified) | Bituminous material oozing from rock in summer | 13 |
| | Hajrul yahood bhasma | Fossil stone occuring as a petrified oblong pointed fruit | 16 |

**Table 2** Hydration regimen

| Drugs | Fluids | Timing (min) |
|---|---|---|
| Potassium chloride (10 mEq) | 500 mL normal saline | 60 |
| Magnesium sulfate (1 g) | 500 mL normal saline | 60 |
| Furosemide (20 mg) | Bolus | |
| Granisetron (3 mg) | | |
| + Dexamethasone (20 mg) | 250 mL normal saline | 30 |
| + Pheniramine | | |
| + Ranitidine | | |
| | 250 mL 10 % mannitol solution | 30 |
| Cisplatin | 500 mL normal saline | 60 |
| | 250 mL 10 % mannitol solution | 30 |
| Potassium chloride (10 mEq) | 500 mL normal saline | 60 |

the 3rd and 6th cycles according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.

### Statistical analysis

Statistical Package for the Social Sciences (SPSS®) version 18.0, IBM Corporation was used for data analysis. Data are presented as mean ± standard deviation for continuous variables and frequency percentage for categorical variables. Independent samples *t* test was used for testing the difference in mean in the two groups. Paired samples *t* test was used to test the mean change in renal function parameters from baseline in response to each chemotherapy cycle in each group. Chi-square test examined proportion independence. Correlations were evaluated using Pearson's correlation analysis. The level of statistical significance was set at $P$ value of <0.05.

## Results

### Patient characteristics

Patient demographic data and chemotherapy regimens administered to the patients are presented in Table 3. Assessment of the relation between the changes in renal function parameters (S. Cr., Cr. Cl., blood urea, and serum cystatin C) after 6th cycle compared to their baseline status, and patient characteristics (age, BSA, performance status, and sex) did not reveal any significant correlation ($P > 0.05$).

### Assessment of renal function

Monitoring of renal parameters throughout the study revealed significant decline in renal function in group "A" compared to cystone-treated group "B" as shown in Table 4. The mean level of S. Cr. and Cr. Cl. showed significant decrease in renal function when compared to their baseline level after each cycle in group "A" ($P < 0.05$). Significant elevation in the mean blood urea level appeared after 3rd, 5th and 6th cycles ($P < 0.001$) in comparison to baseline level in group "A". For all of these parameters (S. Cr., Cr. Cl. and blood urea), no statistically significant change was found after any cycle compared to baseline status in group "B" ($P > 0.05$). The increase in serum cystatin C level compared to baseline level was significant after both 3rd and 6th cycles ($P < 0.001$) in group "A", but only after 3rd cycle ($P = 0.01$) in group "B".

For a number of participants, renal markers values exceeded the normal limits for at least one cycle. As regard S. Cr., Cr. Cl., and serum cystatin C, the number of patients with normal values during all cycles was significantly greater in group "B" (Table 5).

Pearson's correlation analysis showed that prior to the 1st cycle there was a significant negative correlation between Cr. Cl. and S. Cr. level in group "A" ($r = -0.84$, $P < 0.001$) and group "B" ($r = -0.81$, $P < 0.001$). A significant negative correlation was also found between Cr. Cl. and serum cystatin C level in group "A" ($r = -0.45$, $P = 0.03$) and group "B" ($r = -0.65$, $P < 0.001$). After the 6th cycle, there were non-significant negative correlations between Cr. Cl. and S. Cr. level ("A": $r = -0.43$, $P = 0.08$/"B": $r = -0.35$, $P = 0.16$) and between Cr. Cl. and serum cystatin C level ("A": $r = -0.39$, $P = 0.08$/"B": $r = -0.26$, $P = 0.32$).

### Assessment of patient response to cisplatin-based treatment

There was insignificant difference between both groups as shown in Table 6.

#### *Grading of nephrotoxicity*

Group "B" was significantly less affected by nephrotoxicity as shown in Table 7.

**Table 3** Patient demographics and chemotherapy regimens

| Patient characteristics | Study group | | | | Test | |
|---|---|---|---|---|---|---|
| | Group "A" 28 patients | | Group "B" 21 patients | | $\chi^2$* | *P* |
| | No. | % | No. | % | | |
| *Sex* | | | | | | |
| Male | 8 | 28.6 | 9 | 42.9 | 1.08 | 0.30 |
| Female | 20 | 71.4 | 12 | 57.1 | | |
| *Performance status* | | | | | | |
| 1 | 21 | 75 | 17 | 81 | 0.24 | 0.62 |
| 2 | 7 | 25 | 4 | 19 | | |
| *Pathological condition* | | | | | | |
| Non-small cell lung cancer | 16 | 57.1 | 13 | 61.9 | 0.49 | 0.92 |
| Bladder cancer | 5 | 17.9 | 3 | 14.3 | | |
| Head and neck cancer | 4 | 14.3 | 2 | 9.5 | | |
| Gastric cancer | 3 | 10.7 | 3 | 14.3 | | |
| *Chemotherapy regimen* | | | | | | |
| EP (etoposide + cisplatin) | 16 | 57.1 | 13 | 61.9 | 0.49 | 0.92 |
| GemCis (gemcitabine + cisplatin) | 5 | 17.9 | 3 | 14.3 | | |
| PF (cisplatin + 5-fluorouracil) | 4 | 14.3 | 2 | 9.5 | | |
| TPF (docetaxel + cisplatin + 5-fluorouracil) | 3 | 10.7 | 3 | 14.3 | | |
| | Mean | SD | Mean | SD | *t*** | *P* |
| Age (years) | 49 | 12 | 51 | 9 | −0.56 | 0.58 |
| Body surface area (BSA) | 1.8 | 0.1 | 1.8 | 0.2 | −0.11 | 0.92 |
| Dose of cisplatin/cycle (mg) | 125.1 | 10.4 | 125.1 | 12.4 | −0.02 | 0.98 |
| Total dose of cisplatin in 6 cycles (mg) | 750.4 | 62.4 | 750.8 | 74.4 | −0.02 | 0.98 |
| *Baseline renal parameters* | | | | | | |
| S. Cr. (0.5–1.2 mg/dL) | 0.66 | 0.16 | 0.78 | 0.15 | −2.58 | 0.01 |
| Cr. Cl. (≥70 mL/min/1.73 $m^2$) | 104.66 | 23.12 | 89.46 | 21.99 | 2.33 | 0.02 |
| Blood urea (15–45 mg/dL) | 25.46 | 11.13 | 29.81 | 8.38 | −1.50 | 0.14 |
| S. Cystatin C (0.5–0.96 mg/L) | 0.79 | 0.10 | 0.80 | 0.13 | −0.11 | 0.91 |
| *Other baseline laboratory data* | | | | | | |
| Red blood cells (4–6 × $10^{12}$/L) | 4.76 | 0.36 | 4.66 | 0.35 | 0.92 | 0.36 |
| Hemoglobin (12–16 g/dL) | 13.40 | 0.82 | 13.28 | 0.83 | 0.50 | 0.62 |
| White blood cells (4–11 × $10^9$/L) | 8.06 | 1.50 | 7.87 | 1.92 | 0.38 | 0.71 |
| Platelets (150–450 × $10^9$/L) | 314.1 | 73.0 | 297.7 | 82.4 | 0.72 | 0.47 |
| Serum albumin (3.5–5 g/dL) | 3.97 | 0.65 | 4.11 | 0.41 | −0.92 | 0.36 |
| Alanine aminotransferase (10–40 IU/L) | 20.23 | 7.44 | 23.57 | 10.13 | −1.27 | 0.21 |
| Aspartate aminotransferase (10–35 IU/L) | 21.40 | 7.93 | 23.87 | 6.01 | −1.24 | 0.22 |
| Total bilirubin (0.3–1.3 mg/dL) | 0.71 | 0.24 | 0.68 | 0.21 | 0.48 | 0.63 |
| Direct bilirubin (0.1–0.3 mg/dL) | 0.19 | 0.06 | 0.17 | 0.06 | 1.43 | 0.16 |

* $\chi^2$ test, ** *T* test

## Discussion

In this study, we assessed the effect of patient characteristics on the residual nephrotoxic effect of cisplatin after the end of last treatment cycle (i.e. deterioration of kidney function which is expressed by changes in renal function markers after 6th cycle compared to their baseline status). The results did not reveal any significant correlation with patient characteristics (age, BSA, performance status, and sex). This finding is in agreement with previous studies [14, 15]. Other studies had reported the independence of some prognostic indicators (such as BSA and performance

**Table 4** Comparison of renal function markers (mean ± SD) between study groups "A" and "B"

| | S. Cr. (0.5–1.2 mg/dL) | | Cr. Cl. (≥70 mL/min/1.73 m$^2$) | | Blood urea (15–45 mg/dL) | | S. Cystatin C (0.5–0.96 mg/L) | |
|---|---|---|---|---|---|---|---|---|
| | "A" | "B" | "A" | "B" | "A" | "B" | "A" | "B" |
| Baseline | 0.66 ± 0.16* | 0.78 ± 0.15* | 104.66 ± 23.12* | 89.46 ± 21.99* | 25.46 ± 11.13 | 29.81 ± 8.38 | 0.79 ± 0.10 | 0.80 ± 0.13 |
| 1st cycle | 0.83 ± 0.24 | 0.76 ± 0.24 | 86.08 ± 28.66 | 99.49 ± 41.38 | 26.68 ± 8.84 | 27.90 ± 9.95 | – | – |
| 2nd cycle | 0.83 ± 0.20 | 0.85 ± 0.21 | 85.37 ± 27.81 | 82.61 ± 19.81 | 28.11 ± 10.08 | 29.67 ± 14.41 | – | – |
| 3rd cycle | 0.86 ± 0.29 | 0.84 ± 0.27 | 85.64 ± 23.62 | 88.17 ± 32.36 | 32.32 ± 12.31 | 29.10 ± 11.04 | 1.01 ± 0.26 | 0.88 ± 0.19 |
| 4th cycle | 0.87 ± 0.24 | 0.87 ± 0.20 | 85.83 ± 31.51 | 83.01 ± 24.70 | 29.38 ± 8.86 | 31.82 ± 9.72 | – | – |
| 5th cycle | 1.01 ± 0.30* | 0.81 ± 0.22* | 73.12 ± 24.44 | 90.68 ± 30.27 | 32.62 ± 12.17 | 32.24 ± 12.82 | – | – |
| 6th cycle | 1.04 ± 0.21** | 0.78 ± 0.16** | 67.43 ± 14.29** | 91.09 ± 20.33** | 42.14 ± 13.32** | 30.18 ± 10.02** | 1.10 ± 0.27** | 0.81 ± 0.19** |

* $P < 0.05$; ** $P < 0.001$

**Table 5** Patients with renal markers values beyond normal limits

| Renal function parameters | Group "A" | | Group "B" | | $\chi^2$ test | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | $\chi^2$ | *P* |
| *S. Cr.* | | | | | | |
| Normal | 15 | 53.6 | 17 | 81 | 3.97 | 0.04 |
| >1.2 mg/dL | 13 | 46.4 | 4 | 19 | | |
| *Cr. Cl.* | | | | | | |
| Normal | 13 | 46.4 | 16 | 76.2 | 4.40 | 0.04 |
| <70 mL/min/1.73 m$^2$ | 15 | 53.6 | 5 | 23.8 | | |
| *Blood urea* | | | | | | |
| Normal | 16 | 57.1 | 16 | 76.2 | 1.92 | 0.17 |
| >45 mg/dL | 12 | 42.9 | 5 | 23.8 | | |
| *S. Cystatin C* | | | | | | |
| Normal | 13 | 46.4 | 16 | 76.2 | 4.40 | 0.04 |
| >0.96 mg/L | 15 | 53.6 | 5 | 23.8 | | |

**Table 6** Evaluation of patient response to treatment after 3rd and 6th cycles according to RECIST

| Degree of response according to RECIST | Group "A" | | Group "B" | | $\chi^2$ test | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | $\chi^2$ | *P* |
| *3rd cycle* | | | | | | |
| Partial response (PR) | 23 | 82.1 | 16 | 76.2 | 0.26 | 0.61 |
| Stable disease (SD) | 5 | 17.9 | 5 | 23.8 | | |
| *6th cycle* | | | | | | |
| Complete response (CR) | 13 | 46.4 | 14 | 66.7 | 1.99 | 0.16 |
| Partial response (PR) | 15 | 53.6 | 7 | 33.3 | | |

**Table 7** CTCAE grading for AKI applied in both groups "A" and "B"

| Grades of AKI according to CTCAE | Group "A" | | Group "B" | | $\chi^2$ test | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | $\chi^2$ | P |
| Grade 0 | 10 | 35.8 | 16 | 76.2 | 10.75 | 0.01 |
| Grade 1 | 9 | 32.1 | 5 | 23.8 | | |
| Grade 2 | 9 | 32.1 | 0 | 0 | | |

status) from cisplatin nephrotoxicity, but also showed that other factors (such as age and sex) may be correlated to the incidence of toxicity [5, 16].

Throughout the course of the study, values of different parameters used for evaluating renal status showed gradual decline in renal function. However, in most cases, these values remained within the reference limits. This may be due to strict exclusion criteria applied on study candidates, thus patients were selected with normal kidney function

and without comorbidity (such as diabetes or hypertension) or a history of cisplatin administration. For a number of participants in each group, renal function parameters values exceeded the normal limits for at least one cycle but without leading to treatment discontinuation.

Patients in group "A" had significant decline in kidney function in response to cisplatin-based chemotherapy cycles compared to the baseline state, as revealed by all of the measured renal markers (S. Cr. [13], Cr. Cl. [13, 17], blood urea, and serum cystatin C). On the other hand, renal function was relatively spared throughout the study in cystone-treated group "B". Comparing renal function parameters between study groups revealed significantly better renal status in cystone-treated group "B".

Serum cystatin C is a well-known marker for early detection of changes in renal function caused by cisplatin administration [18–22]. In our study, there was a strong negative correlation between Cr. Cl. and serum cystatin C level in group "A" ($r = -0.45$, $P = 0.03$) and group "B" ($r = -0.65$, $P < 0.001$), but the correlation was much stronger between Cr. Cl. and S. Cr. level in group "A" ($r = -0.84$, $P < 0.001$) and group "B" ($r = -0.81$, $P < 0.001$). This finding is in agreement with a recent study carried out by Tezcan et al. [13], while in disagreement with other studies [18, 19].

According to RECIST, there was insignificant difference in treatment response between both study groups after 3rd ($P = 0.61$) and 6th ($P = 0.16$) cycles. According to CTCAE grading for AKI, a significant difference was found between the study groups in favor of cystone-treated group "B" which was less affected by cisplatin-induced kidney injury ($P = 0.01$).

The relatively small population may be a limitation in our study, so large-scale studies are needed to confirm our findings. We also suggest further trials to challenge cystone with greater doses of cisplatin and more cisplatin-based cycles, test the effect of cystone on cisplatin serum level, and evaluate the influence of cystone on other cisplatin side effects. Using other markers to monitor renal status (such as urine lytes or plasma lytes) in future trials may provide additional evidence to the protective effect of cystone. Other studies are also needed to test the efficacy of cystone in cisplatin-treated patients with comorbidities (such as diabetes or hypertension) or with conditions that necessitate coadministration of other nephrotoxic medications. We recommend application of blinding and use of placebo in future studies to provide a stronger design. In conclusion, cystone can be used to protect cancer patients from cisplatin nephrotoxicity, without affecting its antitumor activity. We also recommend cystone to be used as a nephroprotective agent because it is affordable, easily administered, and has no recorded side effects in our study.

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

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