Nephroprotective effect of vitamin E and bismuth combinationation in-Patients treated with cisplatin chemotherapy

Received : 21/2/2011 Accepted: 13/9/2011

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Abstract

Background and objectives: The objective of this study was to explore the optimal combination of agents with their doses used along with cisplatin for the protection of nephrototoxicity.

Method: This experiment was carried out on patients suffering from different types of solid tumors divided into two groups: control group receiving cisplatin in a dose of 90 mg/ m² and the studied group receiving cisplatin in a dose of 90 mg/m² with bismuth subcitrate (200mg/ day) and vitamin E (400mg/day).Blood urea and serum creatinine were tested for the assessments of renal function.

Results: control patients showed a sustain and significant elevation in blood urea and serum creatinine level in comparison with baseline along the entire period of the study, P<0.05. Meanwhile, the effect of cisplatin was shown to be significantly decreased in patients received bismuth-vitamin E therapy (P<0.05) along the entire period of the study.

Conclusion: Bismuth and vitamin E in combination play a beneficial role for preventing cisplatin nephrototoxity. The potentiated actions for preventing cisplatin nephrototoxicity could be achieved via combined use of these agents.

Keywords: Cisplatin; Side effects; Protective agents; Oxidative stress; nephrototoxicity

Introduction

Cisplatin (*cis*-diamine-dichloroplatinum) is a prominent member of the effective broad-spectrum antitumor drugs. However, its clinical usage is restricted due to some adverse side effects, such as ototoxicity and nephrotoxicity. [1–3] Continued aggressive high-dose of cisplatin chemotherapy necessitates the investigation of ways for preventing the dose-limiting side effects that inhibits the cisplatin administration at tumoricidal doses. Until now a large number of studies have been focused on the ways for preventing cisplatin side effects via supplementation of preventive agents simultaneously.[4-6] Although, the mechanism underlying the side effects induced by cisplatin are not understood clearly, it was considered to be attributed to the combination of multi-ways [7–9], such as the generation of reactive oxygen species (ROS), which could interfere with the antioxidant defense system and result in oxidative damage in different tissues [10–12], and reaction with thiols in protein and glutathione, which could cause cell dysfunction. On the other hand, it has been proposed that theantitumor activity of cisplatin was due to its ability to form adducts with DNA, which could cause cross-linking of DNA strands. Metallothionein (MT) is a cysteine-rich protein of low molecular weight and shows high affinity for metals such as zinc, copper, cadmium, mercury, and platinum.[13] One of the proposed biological functions of MT is the detoxication of heavy metals. It has been reported that induction of MT synthesis in animals by administration of heavy metals such as zinc and bismuth can provide protection against the toxic effects of

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Cisplatin. [14-15] Although, the mechanisms involved in the protection of cisplatin nephrotoxicity by MT induction are still unclear, the sequestering of cisplatin or its metabolites by MT molecules and the antioxidant properties of MT have been proposed as possible mechanisms of detoxication.[16-17] As the antitumor activity and side effects of cisplatin- based chemotherapy are mediated in part by different mechanisms, the actions on selective inhibition of certain side effects could be achieved while the antitumor activity was not altered.[18] In this study, I attempted to explore the preventive effect of the combination of these agents for preventing the cisplatin nephrototoxicity.

Method

All patients were informed and signed consent before the study. 60 patients suffering from different types of solid tumors aged between 25-65 years attending Rizgari Teaching Hospital were included in this study, these patients were divided randomly into two groups, the first group represented the control group , 30 patients (12) male, (18) female treated with cisplatin in a dose of 90 mg/ m² at 21days interval and the second group, 30 patients (14) male, (18) female treated with cisplatin in a dose of 90 mg/ m² at 21days interval and bismuth subcitrate (200mg/day) with vitamin E (400mg/day). Blood samples were drawn as a baseline before the initiation of therapy and 21 day intervals after that for three cycles. Each sample was transferred with plastic centrifuge tube, sera were separated by centrifugation at 1000 rpm for 10 minutes and analyzed for urea and creatinine. Blood urea was measured with Reflotron using its special strips, REF 1 1200666. Serum creatinine was measured with Reflotron using its special strips, REF 1 0886874. Statistical evaluation: All data are expressed as mean ± SD. Differences between mean levels with baseline along the entire period of the study were evaluated statistically using students t-test. A value of $P< 0.05$ was considered statistically significant.

Results

1. Blood urea:
The level of blood urea in control patients showed a significant elevation ($P<0.05$) in comparison with baseline values, along the entire period of the study, and reached a maximum level after 63 days (43.33%); meanwhile, patients received bismuth-vitamin E in combination therapy showed a significant elevation in blood urea levels in comparison with baseline values ($P<0.05$), and reached a maximum level after 63 days (15.03%), as shown in Table (1).
2. Serum creatinin:
The level of serum creatinin in control group showed a significant elevation ($P<0.05$) in comparison with baseline values, along the entire period of the study and reached maximum level after 63 days (17.33%); meanwhile, patients received bismuth-vitamin E combination therapy, showed a significant elevation in serum creatinin levels in comparison with baseline values ($P<0.05$), and reached a maximum level after 63 days (6.01%), as shown in Table (2).

Table (1): Blood urea levels in control and patient groups received bismuth-vitamin E in combination therapy.

	Blood urea (15 – 45 mg/dl)			
	Baseline	**After 21 days**	**After 42 days**	**After 63 days**
Control group (n=30)	32.89 ± 11.31	39.47 ± 13.57	45.47 ± 10.67*	47.14 ± 9.94 *
patients group (n=30)	34.93 ± 9.48	37.73 ± 10.24	38.43 ± 10.43 *	40.18 ± 10.91 *
P-value	0.30 [NS]	0.35 [NS]	0.04 [S]	0.03 [S]

Data are expressed as mean ± SD.
n= number of patients.
***P<0.05 with respect to baseline value.**
NS = no significant difference.
S = significant difference.

Table (2):serum creatinin level in control and patient groups received bismuth-vitamin E combination therapy.

	Serum creatinin (0.3 – 1.1 mg/dl)			
	Baseline	**After 21 days**	**After 42 days**	**After 63 days**
Control group (n=30)	0.75 ± 0.25	0.80 ± 0.27	0.87 ± 0.20 *	0.88 ± 0.20 *
patients group (n=30)	0.69 ± 0.2	0.71 ± 0.21	0.72 ± 0.10 *	0.74 ± 0.10*
P-value	0.26 [NS]	0.12 [NS]	0.03 [S]	0.006 [S]

.Data are expressed as mean ± SD.
n= number of patients.
***P<0.05 with respect to baseline value.**
NS = no significant difference.
S = significant difference.

DISCUSSION:

The impairment of kidney function by cisplatin was recognized as the main side effect and the most important dose-limiting factor associated with its clinical use.[19] Nephrototoxicity in this study was gauged by the measurements of blood urea and serum creatinine level. The findings disclosed that each agent used in this study could play a beneficial role for preventing cisplatin nephrototoxicity; however none could play the crucial role. Metallothionein (MT) is a protein with low molecular weight, and one-third of its amino acids are cysteine residues therefore, can easily trap and sequester metal ions with its thiols. MT was reported to be the main mechanism underlying the action of bismuth against cisplatin toxicity. [20-21]Several studies in vitro have shown that, the elevation of MT levels in certain cultured cells can induce resistance to cisplatin. [22-23] It has been reported that the active metabolites of cisplatin cauld react quickly with the thiols in glutathione (GSH) and small proteins such as MT, then in high molecular weight proteins such as albumin through covalent link. Thereby, the levels of GSH and MT cauld play an important role in .

switching the mode of cell death induced by cisplatin. [24] On the other hand, it has been reported that intracellular levels of GSH and induction of MT were directly involved in the resistance toward cisplatin in tumor cells. [25-27] It has recently been shown, that pretreatment with bismuth compounds reduced markedly the toxic side effects of various anticancer drugs such as cisplatin [28-30], Adriamycin [30-31] and bleomycin [32], tumor necrosis factor [33], and -y-irradiation [34] without compromising their antitumor activities. Bismuth compounds induce specifically MT synthesis in normal tissues such as kidney, liver, heart, and bone marrow but not in tumors. [28-29, 35]
There were many studies which have demonstrated the involvement of oxidative stress, lipid peroxidation and mitochondria dysfunction in CP-induced nephrotoxicity. [36-40] A mechanism by which CP exerted its cytotoxicity was through the generation of reactive oxygen species (ROS). [40-41] The administration of CP caused an increase in lipid peroxide levels and a decreased in the activity of antioxidant defense enzymes, as well as in the concentrations of non-enzymatic components of anti oxidative stress that prevented, or protected against lipid peroxidation in the tissues. [42] It was accepted that both correlated to oxidative stress and caused an imbalance between the generation of oxygen derived radicals and the organism's antioxidant potential [43].
Supplementation of the antioxidant vitamin E has been reported to inhibit lipid peroxide in various conditions such as CP-induced nephrotoxicity and hepatotoxicity [42].Recent studies have focused on the role of antioxidants in CP toxicity. Administration of antioxidants such as vitamin E and vitamin C before and during treatment with CP has been used to protect against toxicity in humans and experimental animals. [38,42, 44-46]
In conclusion, the findings of this study would provide a more promising strategy for preventing nephrototoxicity of cisplatin-based chemotherapy. However, this study was a pilot study and the results were preliminary, starting with bismuth and vitamin E in combination therapy before the initiation of cisplatin therapy might be of an additional benefit and I recommended an additional studies using other combination of agents on a large number of patients.

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