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Renal protection with magnesium subcarbonate and magnesium sulphate in patients with epithelial ovarian cancer after cisplatin and paclitaxel chemotherapy: A randomised phase II study

Lubomir Bodnar[a,*], *Gabriel Wcislo*[a], *Agnieszka Gasowska-Bodnar*[b], *Agnieszka Synowiec*[a], *Katarzyna Szarlej-Wcisło*[a], *Cezary Szczylik*[a]

[a]*Department of Oncology, Military Institute of The Health Services, 128 Szaserow Street, 00-909 Warsaw, Poland*
[b]*Department of Gynaecological Oncology, Military Institute of The Health Services, Warsaw, Poland*

ARTICLE INFO

Article history:
Received 17 June 2008
Received in revised form 24 July 2008
Accepted 5 August 2008
Available online 14 September 2008

Keywords:
Cisplatin
Magnesium
Ovarian cancer
Renal function
Side effect

ABSTRACT

Background: The aim of this study was to examine the effect of magnesium supplementation on nephrotoxicity accompanying standard cisplatin-based chemotherapy in patients with epithelial ovarian cancer (EOC).

Patients and methods: A double-blind, placebo-controlled, randomised study was conducted in which study arm magnesium sulphate (5 g) was administered before each course of standard chemotherapy with paclitaxel (135 mg/m^2/24 h) plus cisplatin (75 mg/m^2) every 3 weeks in patients with EOC. Magnesium subcarbonate (500 mg), three times per day orally, was administered during the treatment intervals. The control arm was administered a placebo instead of both magnesium salts. Magnesium serum levels (sMg) and GFR markers: serum levels of creatinine (sCr), Cockroft–Gault (ClCG) and Modification Diet of Renal Disease (MDRD) formulae were recorded before each cycle, and 3 weeks after the sixth course.

Results: 41 EOC patients were randomised and 40 were eligible. sMg varied significantly between the supplemented and placebo groups ($p<0.0001$). The control group showed a significantly greater decrease of GFR assessed by: sCr ($p = 0.0069$), ClCG ($p = 0.0077$) and MDRD ($p = 0.032$) formulae compared with the magnesium supplemented group.

Conclusions: These results demonstrate the nephroprotective effect of magnesium supplementation during chemotherapy with cisplatin.

1. Introduction

Ovarian cancer is the most common cause of death among women with gynaecologic malignancies. Poor treatment results (i.e. 5-year survival approximately 50%) are mainly caused by the advanced stage noted at the time of diagnosis. In most instances, treatment for ovarian cancer includes primary surgery followed by systemic chemotherapy. The standard chemotherapy consists of a platinum analogue (carboplatin or cisplatin) combined with paclitaxel.[1,2] The efficacy of combined chemotherapy is highly related to the amount of residual tumour left after surgery.

* *Corresponding author:* Tel.: +48 22 6817110; fax: +48 22 6817110.
E-mail address: lubo@esculap.pl (L. Bodnar).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2008.08.005

Nephrotoxicity is a well-known side effect of cisplatin treatment. Though not necessarily dose limiting, renal toxicity still affects the majority of patients and a significant decrease in glomerular filtration rate is observed during treatment.[3] Logistic regression analyses have shown that the risk factors for nephrotoxicity development include older age, female gender, smoking, hypoalbuminaemia and paclitaxel coadministration. The nephrotoxic damage appears to be a clinical problem in 28–42% of patients applied cisplatin.[4,5] The principal site of damage is the proximal tubule in the outer renal medulla, particularly in the S3 segment and in the thick ascending limb of the loop of Henle or in the distal parts of the nephron segments.[6] Several mechanisms contribute to dose-dependent and cumulative cisplatin-induced nephrotoxicity: DNA damage, oxidative stress, inhibition of protein synthesis, mitochondrial dysfunction, and involvement of receptors of the tumour necrosis factor (TNF) family and apoptosis of the renal epithelial cells.[7–9]

Great electrolyte abnormalities are often emerged from tubular reabsorption defects. One of them is hypomagnesaemia, initially described by Schilsky and Anderson in 1979.[10] Renal tubular toxicity provides a mechanistic explanation. Sobrero and colleagues[11] suggested that the active transport mechanism may become saturated, leading to an overconcentration of cisplatin in tubular cells with subsequent cellular necrosis. Magnesium and calcium are involved in the active cisplatin transport system, and decreasing their concentrations may contribute to the intensification of cisplatin toxicity effects toward the tubular cell in the kidney. One recent study has suggested that magnesium salt supplementation is a crucial factor in protection against the nephrotoxic actions of Cyclosporin A (CsA) in cell lines isolated from rat proximal tubules.[12] It was demonstrated that low serum magnesium levels are associated with a faster rate of decline in kidney allograft function and increased rates of graft loss in renal transplant recipients with chronic CsA nephropathy.[13] An experimental rat model study has indicated a substantial additive effect of magnesium-depletion on cisplatin induced renal toxicity as evidenced by significant changes in plasma creatinine and urea, renal failure induced mortality and loss of renal transporters. This should shed light on the nephrotoxicity observed during cisplatin treatment which might be substantiated by the known magnesium-loss associated with cisplatin treatment, particularly in patients affected by severe gastrointestinal side effects.[14]

The aim of this study was to examine the effect of magnesium supplementation on nephrotoxicity accompanying standard cisplatin-based chemotherapy in patients with ovarian cancer, and to assess the impact of this strategy on the outcome and toxicity of treatment.

2. Patients and methods

This prospective study included consecutive patients with ovarian cancer, after primary surgery, who qualified for first-line chemotherapy. The study protocol was approved by the local Ethics Committee, and written informed consent was obtained from all participants of the study.

Patients were assigned to receive six courses of the standard, first line chemotherapy consisting of 135 mg/m^2 of intravenous infusion paclitaxel over a 24-h period on day 1 followed by 75 mg/m^2 of intravenous infusion cisplatin on day 2. Standard premedication (dexamethasone 20 mg, ranitidinum 50 mg, clemastinum 2 mg) was given intravenously to prevent hypersensitivity reactions to paclitaxel. Treatments were administered every 3 weeks for six cycles.

Patients were randomly assigned to magnesium sulphate as 5 g iv infusion with prehydration before each cycle of chemotherapy with a continuation of magnesium subcarbonate supplementation, 500 mg three times daily given orally, between cycles of chemotherapy and 3 weeks after the sixth chemotherapy course, or placebo. Doses of magnesium sulphate given intravenously were adopted from the prospective study of Ashraf M and colleagues[15] and the dose of magnesium subcarbonate was equivalent to that used by Martin and colleagues.[16] Hydration and antiemetic agents (Ondansetron 8 mg) were given before the administration of cisplatin. To receive a subsequent cycle of chemotherapy, patients were required to have an absolute neutrophil count of 1.5×10^9/l cells per cubic millimetre or greater, a platelet count of $>100 \times 10^9$/l and a creatinine clearance of > 0.83 ml/s. Treatment modifications for haematological toxic effects included cycle delay dose reduction or the addition of granulocyte colony-stimulating factor. The treatment was postponed in a case of grade 3 or 4 peripheral neuropathy or when the creatinine clearance reached less than 0.83 ml/s.

GFR markers as: serum levels of creatinine, Cockroft–Gault (ClCG) and Modification Diet of Renal Disease (MDRD) formulae were recorded before each cycle of chemotherapy, and 3 weeks after the sixth cycle. We decided to assess GFR by using two formulae, MDRD and ClCG, because they provide useful and acceptable estimates of GFR in adults in an independent manner (level A recommendation of clinical practice guidelines by the National Kidney Foundation).[17]

2.1. Laboratory methods

A COBAS INTEGRA 800 (Roche Diagnostics) automated analyser was used to determine serum creatinine, albumin, BUN, and magnesium concentrations by using commercial kits.GFR was calculated from the Cockroft–Gault formula: $GFR = \frac{140 - age(years) \times weight(kg) \times k}{72 \times Cr(\mu mol/l)}$, where k is 1.23 for men and 1.04 for females; Cr is serum creatinine level.GFR was calculated from the MDRD formula as:GFR = 170 × [serum creatinine level (mg/dL)]$^{-0.999}$ × [age (years)]$^{-0.176}$ × [0.762 for women] × [1.18 for black women] × [BUN]$^{-0.170}$ × [ALB]$^{0.318}$

All values we converted from conventional units to SI units.

2.2. Safety assessment

All patients who received more than one cycle of chemotherapy cisplatin/ paclitaxel were eligible for the toxicity assessment. Haematological and non-haematological toxicity were assessed through review of laboratory reports including haemoglobin concentration, neutrophil counts, leucocyte counts, platelet counts and medical records. Haematological and non-haematological toxicities were gradated using the

common terminology criteria for adverse events of the National Cancer Institute's Common Toxicity Criteria v. 3.0.[18]

2.3. Statistical analysis

Demographic data are presented as median or mean with standard deviation (SD) and 95% confidence interval (CI). Variables before treatment were compared with Student *t*-test or Mann–Whitney test, where appropriate. Mean values of GFR markers from seven samples were analysed by magnesium supplementation status using repeated-measures by ANOVA test. When the ANOVA test resulted in a significant effect on treatment, we had them compared by using the Tukey Honestly Significant Difference (HSD) post hoc test to show differences between means. Correlations were assessed by nonparametric Spearman correlation test.

Overall survival (OS) was defined as time elapsed between the date of randomisation and date of death or the date of last follow-up. Time to progression (TTP) was calculated from the date of randomisation to the first documented evidence of treatment failure; patients who were still alive without progressive disease at the time of analysis were censored on the date of their last follow-up. Mann–Whitney U test was used to compare toxicity and efficacy between groups with regard to magnesium salt supplementation. Median and life tables were computed using the product-limit estimate by the Kaplan and Meier method and the log-rank test was employed to assess the statistical significance; p values less than 0.05 were considered to indicate statistical significance. Statistical calculation was performed using the STATISTICA for Windows Version 7.0 software.

3. Results

3.1. Study population

Between January 2003 and January 2006, 41 women were randomly assigned: 20 and 21 women to the supplemented (study) and placebo (control) groups, respectively. One patient from the placebo group was ineligible for analysis because she withdrew the consent of participation in this study during the first cycle of chemotherapy. Table 1 shows the characteristics of the 40 eligible patients whose data form the basis of this report. There were no significant differences between both groups in clinical and pathological parameters and markers of GFR such as: serum levels of creatinine, ClCG and MDRD formulae denoted before chemotherapy.

3.2. Changes of magnesium serum levels during chemotherapy

We noted significant differences in magnesium serum levels during chemotherapy between the supplemented and placebo groups ($p<0.0001$). Subsequent post hoc analysis of magnesium serum levels revealed that measurements obtained before each cycle and 3 weeks after the sixth course in the placebo group had significantly decreased levels of magnesium serum in successive measurements. In the magnesium supplemented group, no significant differences in magnesium serum levels occurred during treatment (Fig. 1).

3.3. Renal function during chemotherapy

Serum creatinine levels during chemotherapy between supplemented and placebo groups differed significantly ($p = 0.0069$). Post hoc analysis of serum creatinine levels revealed that measurements from III to VI in the placebo group increased significantly from the baseline value before chemotherapy started. In the supplemented group there were no significant differences in creatinine serum levels during treatment.

Cockroft–Gault formula during chemotherapy between supplemented and placebo groups showed GFRs altered significantly ($p = 0.0077$). Subsequent post hoc analysis of GFR calculated by ClCG revealed that measurements after the first and up to the last (3 weeks after the sixth cycle of chemotherapy) in the placebo group significantly decreased GFR from the first values. No such differences were seen in the supplemented group.

MDRD formula during chemotherapy showed significantly different values between the supplemented and placebo groups ($p = 0.0324$). Post hoc analysis of MDRD values identified significant differences in measurements from III to VI obtained in the placebo group compared with the baseline value before chemotherapy started. In the supplemented group we did not observe any significant difference in GFR assessed by the MDRD formula during treatment (Table 2).

3.4. Toxicity profile

All 40 patients were evaluated for safety and tolerability. A total of 1299 cycles of chemotherapy (paclitaxel/ cisplatin) were administered. The median number of cycles of cisplatin/ paclitaxel was 6, range 1–6. In 10% of patients (4/40), therapy with cisplatin was stopped early because of renal toxicities (decrease GFR more than 0.83 ml/s). There were no treatment related deaths.

The main toxicities consisted of haematological adverse effects. Grade 3/4 neutropenia was experienced by 50% of patients, grade 3/4 leucopenia by 45%, grade 3/4 anaemia by 5%, and grade 3/4 thrombocytopenia by 2.5% of patients. The only difference in haematological toxicity profile was that anaemia was more frequently seen in the placebo group (85%) than in the supplemented one (55%) and this phenomenon was statistically significant (Mann–Whitney U test; $p = 0.037$, Table 3).

Non-haematological toxicity included grade 3 alopecia in 92.5% of patients, nausea grade 3 in 30%, grade 3 vomiting in 15%, grade 2–3 diarrhoea in 15%, and grade 2–3 constipation in 30%. Non-haematological toxicity and treatment outcomes were not different in either group of patients (Table 4).

3.5. Survival

There was no difference in time to progression between the supplemented and control groups (median TTP - 20.9 and 14.8 months, respectively; log-rank test, $p = 0.78$; Fig. 2A), and neither there was a difference in overall survival (log-rank test, $p = 0.28$; Fig. 2B).

Table 1 – Patient characteristics (N = 40)

Characteristic	Supplemented group (No = 20/40)		Control group (No = 20/40)		P value*
	No.	%	No.	%	
Age, years					
Median	53		54		0.705
95% CI	50–56		46–56		
BSA (m^2)					
Mean, SD	1.67 ± 0.12		1.76 ± 0.16		0.09
95% CI	1.62–1.73		1.68–1.84		
PS (ECOG)					
0	8	20%	3	7.50%	0.262
1	11	27.50%	17	42.50%	
2	1	2.50%	–	–	
Stage at diagnosis (FIGO)					
I	4	10%	1	2.50%	0.256
II	–	–	1	2.50%	
III	14	35%	16	40%	
IV	2	5%	2	5%	
Histology:					
serous	13	32.50%	14	35%	0.473
endometrial	5	12.50%	5	12.50%	
clear-cell	1	2.50%	1	2.50%	
mucinous	1	2.50%	–	–	
Primary surgery:					
Primary radical	4	10%	2	5%	0.285
Optimal debulking	6	15%	4	10%	
Suboptimal debulking	10	25%	14	35%	
Creatinine					
Mean, SD	59.23 ± 13.26		55.69 ± 11.49		0.434
95% CI	52.16–65.42		50.39–60.99		
ClCG					
Mean, SD	1.65 ± 0.40		1.95 ± 0.56		0.059
95% CI	1.47–1.84		1.69–2.21		
MDRD					
Mean, SD	1.68 ± 0.37		1.81 ± 0.51		0.366
95% CI	1.51–1.85		1.57–2.05		
ALB					
Mean, SD	39.8 ± 5.4		39.8 ± 4.4		0.998
95% CI	37.3–42.4		37.8–41.9		
BUN, SD					
Mean, SD	4.98 ± 2.36		4.52 ± 1.44		0.458
95% CI	3.87–6.09		3.84–5.19		
Magnesium					
Mean, SD	0.90 ± 0.04		0.87 ± 0.04		0.058
95% CI	0.88–0.92		0.85–0.89		

Abbreviations: FIGO - International Federation of Gynaecology and Obstetrics, PS - performance status, ECOG - Eastern Cooperative Oncology Group, BSA - body surface area, SD - standard deviation, CI - confidential interval. *$p<0.05$ with the U Mann– Whitney test or Student t-test, where appropriate.

4. Discussion

Cisplatin appears to be a very important cytostatic agent but has numerous side-effects including a paramount one, nephrotoxicity, which has attracted much attention as the major dose-limiting factor. The mechanism by which cisplatin selectively does harm to renal tubular cells has not yet been fully elucidated. Similar to several nephrotoxic heavy metals, cisplatin may accumulate in the kidney to interact with sulfhydryl groups, following the increased membrane fragility and depletion of intracellular glutathione. Towsend and colleagues[19] have shown that the nephrotoxicity of cisplatin is the result of the metabolic transformation of cisplatin in the kidney to potentially more toxic substances. Two enzymes expressed in the proximal tubules, i.e. gamma-glutamyl transpeptidase (GGT) and cysteine-S-conjugate beta-lyase, have a pivotal role in renal toxicity.[5–7] Ciarimboli and colleagues[20] have identified the human organic cation transporter 2 (hOCT2) as the critical mechanism responsible for cisplatin nephrotoxicity in isolated human proximal tubules.

The aim of our study was to examine the effect of magnesium supplementation on nephrotoxicity accompanying standard cisplatin-based chemotherapy in patients with ovarian cancer. These results demonstrate the nephoprotective effect of magnesium supplementation during chemotherapy with cisplatin/paclitaxel. In the magnesium supplemented arm, there was no significant decrease of GFR, as assessed by creatinine serum levels, ClCG and MDRD formulae, in

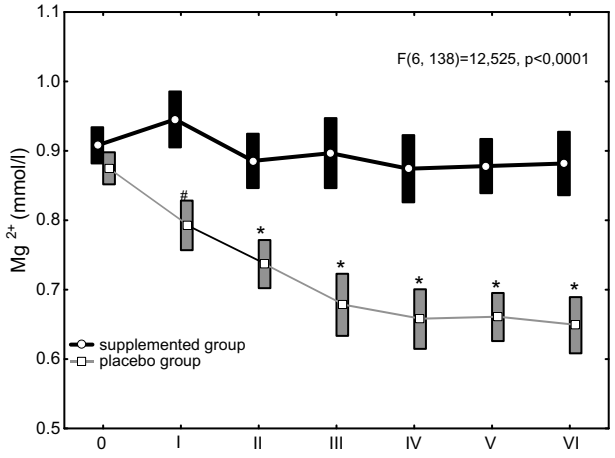

Fig. 1 – Serum levels of magnesium in both the supplemented and placebo groups (0 - before treatment [baseline]; I,II,III,IV,V,VI - after each cycle of chemotherapy; # statistical significance at the level of $p<0.01$; * statistical significance at the level of $p<0.001$).

comparison with the placebo arm. Our results are in accordance with the results presented by Willox and colleagues[21] where they demonstrated reduced renal tubular damage and fewer postponed days to treatment continuation following supplementation with magnesium salt in cancer patients administered cisplatin chemotherapy.

The preventive effects of magnesium salt supplementation against cisplatin- induced nephrotoxicity may be related to a number mechanisms as yet not known in- depth. Cisplatin has multiple intracellular effects, including regulation of expression of many genes, causing direct cytotoxicity with reactive oxygen species. Other mechanisms spread to activate mitogen-activated protein kinases, promotion of apoptosis, and stimulation of inflammation and fibrogenesis.[22] Yuan and colleagues[23] have recently studied the role of magnesium salt supplementation on the development of Cyclosporine A induced nephrotoxicity in rats. Dietary supplementation with magnesium seems to improve renal function and almost abolishes CsA-induced histological lesions via alteration of the abnormal activation of constitutive nitric oxide synthase in this model. Layer and colleagues[14] have focused on the role of magnesium in renal function alteration during cisplatin treatment. Rats had access to either a diet with standard magnesium or to a magnesium depleted diet. The cisplatin treatment caused a significant increase in both plasma creatinine and urea in the Mg-deficient rats, with severe renal failure. The rats on a standard Mg-intake had normal plasma concentrations of creatinine and urea throughout the 3-week experimental period. Vehicle treated rats on the Mg-deficient diet, like the cisplatin treated rats, developed significant hypomagnesaemia, but plasma creatinine and urea were unchanged throughout the experimental period.

Several supportive steps of proper management have been proposed to prevent cisplatin-induced nephrotoxicity with

Table 2 – Renal toxicity

Cycles	Creatinine (mmol/l)		ClCG (ml/s)		MDRD (ml/s)	
	S	C	S	C	S	C
0	59.23±13.29	55.69± 11.49	1.65± 0.40	1.95± 0.56	1.68± 0.37	1.81 ± 0.51
I	61.88±21.22	65.42±11.49*	1.58± 0.41	1.65±0.44*	1.66±0.46	1.51±0.35 *
II	59.23±11.48	63.65±11.48	1.61± 0.43	1.69±0.38*	1.73±0.35	1.56±0.29
III	60.11±13.26	65.42±10.61*	1.58± 0.38	1.65±0.40*	1.70±0.42	1.50±0.30*
IV	61.88±9.72	69.84±14.14**	1.53± 0.33	1.57±0.46**	1.60±0.29	1.41±0.33**
V	63.65±12.38	72.49±15.03**	1.49±0.36	1.41±0.42**	1.56±0.31	1.34±0.32**
VI	72.49±30.06	81.33±20.33**	1.51±0.43	1.38±0.43**	1.48±0.43	1.20±0.35**

Abbreviations: Data are expressed as mean concentrations ± SD (standard deviations); 0 - before treatment (baseline); I,II,III,IV,V,VI after each cycle of chemotherapy; ClCG - Cockroft–Gault formula; MDRD - Modification Diet of Renal Disease formula; S - magnesium salt supplemented group; C - control group (placebo).
* = $p < 0.05$ and ** = $p < 0.001$ ANOVA, post hoc Tukey HSD revealed significant variances in the concentration of these parameters, including the base-line measurement (0), across the treatment period.

Table 3 – Haematologic toxicity

Toxicity (No = 40)	CTC NCI Grade								U	P value
	I		II		III		IV			
	S	C	S	C	S	C	S	C		
Anaemia	25% 5/20	20% 4/20	25% 5/20	60% 12/20	5% 1/20	5% 1/20	-	-	123.0	0.037*
Thrombocytopenia	5% 1/20	10% 2/20	–	–	5% 1/20	–	–	–	198.0	0.956
Leukopenia	10% 2/20	10% 2/20	15% 3/20	20% 4/20	35% 7/20	20% 4/20	10% 2/20	25% 5/20	160.0	0.279
Neutropenia	15% 3/20	15% 3/20	15% 3/20	10% 2/20	5% 1/20	25% 5/20	45% 9/20	25% 5/20	194.5	0.881

Abbreviations: S - magnesium salt supplemented group; C - control group (placebo); * difference is statistically significant.

Table 4 – Non-haematologic toxicities occurring in more than 10% of patients treated with Paclitaxel/Cisplatin (N = 40)

Toxicity (n = 40)	CTC NCI Grade								U	P value
	I		II		III		IV			
	S	C	S	C	S	C	S	C		
Vomiting	15% 3/20	10% 2/20	35% 7/20	50% 10/20	15% 3/20	15% 3/20	–	–	175.0	0.50
Nausea	10% 2/20	10% 2/20	65% 13/20	55% 11/20	25% 5/20	35% 7/20	–	–	183.0	0.65
Diarrhoea	30% 6/20	30% 6/20	15% 3/20	10% 2/20	–	5% 1/20	–	–	184.0	0.87
Constipation	20% 4/20	10% 2/20	25% 5/20	30% 6/20	5% 1/20	–	–	–	191.0	0.81
Alopecia	5% 1/20	–	–	5% 1/20	90% 18/20	95% 19/20	–	–	189.0	0.77
Ototoxicity	5% 1/20	–	55% 11/20	55% 11/20	–	–	–	–	195.5	0.90
Sensory neurotopathy	70% 14/20	55% 11/20	15% 3/20	15% 3/20	5% 1/20	–	–	–	174.5	0.49
Motor neurotopathy	60% 12/20	55% 11/20	15% 3/20	15% 3/20	5% 1/20	–	–	–	157.5	0.25
Stomatitis	20% 4/20	10% 2/20	5% 1/20	5% 1/20	–	–	–	–	171.5	0.44
Cardiac	25% 5/20	20% 4/20	20% 4/20	15% 3/20	–	–	–	–	180.5	0.60
Creatinine	5% 1/20	15% 3/20	–	–	–	–	–	–	180.0	0.59

Abbreviations: S - magnesium salt supplemented group; C - control group (placebo).

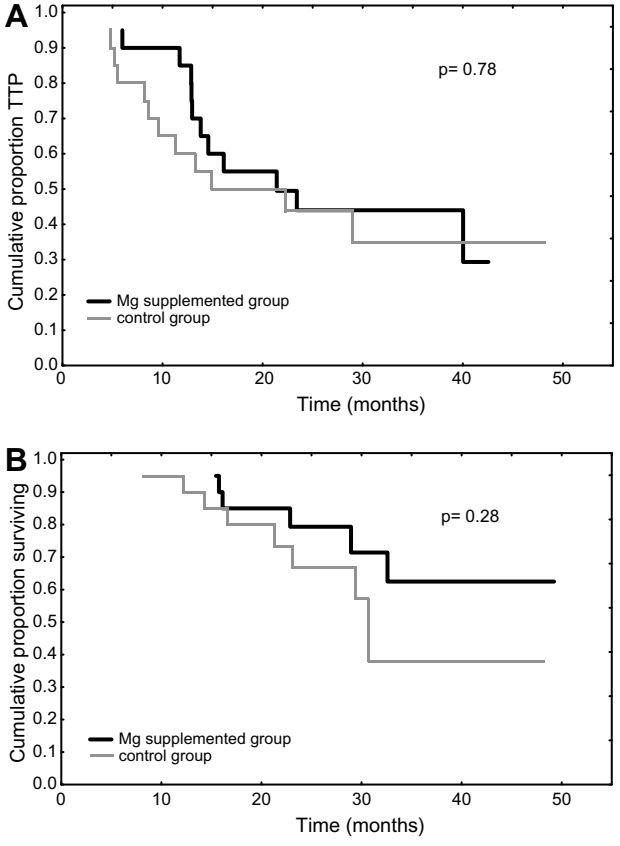

Fig. 2 – (A) Time to progression (TTP) in the magnesium salt (Mg) supplemented group and the control group (placebo); (B) overall survival (OS) in both groups.

the mainstay relying on adequate hydration before and during cisplatin administration, combined with osmotic diuretic agents such as mannitol (the current standard method). Moreover, the utility of nephroprotective agents such as organic thiosulphate compounds, theophylline, amifostine and silibinin have been investigated in this setting.[24–27]

Amifostine is a pro-drug that is dephosphorylated by the enzymatic mechanism to form its active metabolites. Therefore, differences between the alkaline phosphatase to form its activity in tumour tissues or normal tissues are able to result in greater conversion of amifostine to active metabolities in the latter. Inside the cell, the free thiol provides an alternative target to DNA and RNA for the reactive molecules of alkylating or platinum agents and acts as a potent scavenger of the oxygen free radicals induced by ionising radiation and some anticancer drugs. In two randomised trials, Hartmann and colleagues[28,29] have shown that intravenous aminofostine applied before cisplatin or carboplatin administration preserved GFR measures with creatinine clearance report. Amifostine is a rather costly drug to use in clinical practice especially when its cost is compared to costs of chemotherapeutic agents. On the other hand, magnesium salt supplementation seems to be effective in terms of renal protection management with less cost.

There is concern for the role of magnesium salt supplementation in modification of chemotherapy efficacy. We did not show any evidence of worse treatment results in the study group in which patients were given magnesium salt supplementation. However, we are still aware of the weakness of our trial in that the small number of patients does not allow us to draw meaningful conclusions.

In conclusion, our study indicates that magnesium supplementation during chemotherapy with cisplatin/ paclitaxel in patients with ovarian cancer provides renal protection with no apparent reduction of antitumour effects. Therefore, further phase III study and experimental investigations should be carried out to examine the clinical role and exact mechanisms which are responsible for the protective effects of magnesium salts in cancer patients who are given nephrotoxic cisplatin.

Conflict of interest statement

None declared.

Acknowledgement

Support from the Military Institute of The Health Services, Warsaw, Poland, Grant No. WIM-1231/2004.

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