Life Science Informatics Publications

Research Journal of Life Sciences, Bioinformatics, Pharmaceutical and Chemical Sciences

Journal Home page http://www.rjlbpcs.com/

RJLBPCS

ISSN 2454-6348

Original Research Article **DOI - 10.26479/2017.0303.08**

SERUM MAGNESIUM LEVELS IN CERVICAL CANCER PATIENTS ON CISPLATIN BASED CHEMOTHERAPY AT PARIRENYATWA GROUP OF HOSPITALS, ZIMBABWE

Nyasha Elizabeth Kamanga[1], Danai Tavonga Zhou[1,2]*

1. Department of Medical Laboratory Sciences, University of Zimbabwe, College of Health Sciences
2. Department of Health Sciences, Africa University, College of Health, Agriculture and Natural Sciences

ABSTRACT: Background: Hypomagnesaemia is a common side effect of cisplatin-based chemotherapy in cancer patients and cisplatin dose per cycle determines the degree of hypomagnesaemia. This longitudinal study detected hypomagnesaemia in cervical cancer patients over eight weeks' follow-up. **Methods:** Female cervical cancer patients (N=82), mean age 56.3±12.7 years, beginning cisplatin-based chemotherapy during the study were enrolled. At follow-up all patients had received at least four cycles of cisplatin-based chemotherapy. Group 1 patients (n=51) were receiving low weekly cisplatin dose of 50mg/m^2 while 31 patients receiving moderately high weekly cisplatin dose of 75mg/m^2 comprised Group 2. **Results:** Mean magnesium level for all patients was 0.92±0.23mmol/L at baseline and this was within normal range, as were mean magnesium levels for patients in Group 1 (0.93±0.25mmol/L) and Group 2 (0.92±0.02mmol/L). After administration of cisplatin-based chemotherapy for eight weeks, there was significant decline in magnesium levels for both groups of patients ($p<0.0001$) and mean levels became mildly hypomagnesaemic. There was no difference in magnesium at baseline and follow-up for Group 1 and 2 patients. **Conclusion:** Cisplatin based chemotherapy was associated with lowering of mean magnesium levels to mildly hypomagnesaemic levels, in cervical cancer patients, after eight weeks of therapy in patients treated at Parirenyatwa Group of Hospitals in Harare, Zimbabwe between November 2015 and April 2016. This study confirms the findings of previous studies that indicate that cisplatin is associated with development of hypomagnesaemia. However the decline in magnesium was not dose dependent in contrast to reports from similar studies.

KEYWORDS: Cervical Cancer; Cisplatin; Magnesium; Zimbabwe

*** Corresponding Author: Dr. Danai Tavonga Zhou, Ph.D.,** Email Address: danaizh@yahoo.co.uk

Department of Medical Laboratory Sciences, University of Zimbabwe, College of Health Sciences

Department of Health Sciences, Africa University, College of Health, Agriculture and Natural Sciences

1. INTRODUCTION

Cancer is the uncontrolled growth of cells, and is capable of invading and spreading to distant sites of the body [1]. Environmental factors lead to accumulation of mutations in the genes that control the growth rate of cells: the oncogenes and genes that help to prevent cancer: the tumour suppressor genes [2, 3]. Modern oncology research suggests that the damage to the genetic apparatus of the cell is the main cause of cancer and that pathogenesis of cancer involves transformation of a normal cell into a tumour cell at the cellular, molecular and genetic levels of the organism [4, 5]. There are three environmental causes of cancer: chemical carcinogens e.g benzypyrene, asbestos; physical carcinogens e.g. ionizing radiation, ultraviolet radiation and biological carcinogens e.g. bacteria, viruses [6]. For example, human papilloma virus (HPV) releases a viral E6 protein which plays an important role by blocking the apoptosis that would normally occur in body cells [6]. Cancer is a worldwide disease and one of the leading causes of morbidity and mortality in the developed world. Based on present trends, projections strongly suggest an expected yearly incidence of 15 to 20 million new cases worldwide with a 50 to 60% rise occurring in the developing world [7]. Cancer has severe health consequences accounting for 7.6 million deaths (about 13% of all deaths) in 2008 and is estimated to continue rising, with about 13.1 million deaths in 2030 [8]. Amongst Zimbabweans the total number of new cancer cases recorded in 2013 was 6548 [9]. Frequently occurring cancers among Zimbabweans of all races include cervical cancer (18%), Kaposi sarcoma (10%), breast (7%), prostrate (7%), non-Hodgkin's lymphoma (6%), non-melanoma skin cancer (6%), oesophagus (4%), colorectal (4%) and eye cancer (3%). Other cancers account for 35% of the registered cancers in Zimbabwe [9]. Cervical cancer is highly destructive to women's health all over the world, more so in developing countries, where it is leading cause of death in women [10]. It is projected that 500 000 new cervical cancer cases occur every year all over the world, 80% of the cases being in the developing world [11]. Although cervical cancer is a preventable disease, it remains a major burden on public health resources especially in sub-Saharan Africa [10]. Countries in this region have some of the world's age standardized death rates from cervical invasive cancer, such as 67 per 100 000 in Harare, Zimbabwe [12] and 40.8 per 100 000 in Kampala, Uganda in 1997 [13]. In Zimbabwean black women, cervical cancer is the most common cancer affecting 32.1% of the female population [9]. Almost all cases of cervical cancers are due to infection with high risk human papilloma virus (HPV) HPV 16 and HPV18 [14]. Other risk factors include smoking (which decreases the number of macrophages in the body) and HIV infection (which causes immunosuppression) [15].Cisplatin is a major antineoplastic drug used for the treatment of solid tumours [16]. Cisplatin, also known as cis-diamminechloroplatinum II (cisplatinum), DDP, Platinol-AQ, or CDDP is a widely used cytotoxic agent with a broad range of actions and the indications of cisplatin include treatment of solid tumours such as lymphomas, endometrial neck, cervical, head, urothelial, testicular, bladder, lung, and ovarian

cancer [17]. The discovery of cisplatin as an anticancer drug in the 1960s opened a new era in cancer treatment [18]. Clinical use of cisplatin ensured that many patients with different types of cancer were successfully treated and received a better prognosis and the cancer became less life-threatening [19, 20]. Cisplatin reacts with DNA and activates irreversible apoptotic programme of the cell resulting in cell death [21]. The major toxicities of cisplatin are nausea, vomiting and a high incidence of renal dysfunction. Renal toxicity is a common and dose-limiting side effect of cisplatin. Renal tubular damage is a cisplatin recognised mechanism of toxicity [22]. Almost 20% of patients receiving high dose cisplatin have severe renal dysfunction [16]. Cisplatin causes hypomagnesaemia due to this renal tubular damage and urinary magnesium wasting which occurs in 40-100% of patients on cisplatin based chemotherapy [23, 24]. To avoid tetany, routine monitoring of magnesium is recommended [25]. Electrolyte disturbances such as hypophosphataemia, hypocalcaemia, hypokaelamia and hypomagnesaemia are common with cisplatin treatment. The electrolyte disturbances together with renal damage may be associated with focal necrosis at major parts of the nephron caused by cisplatin [26]. The cisplatin concentration in the proximal tubular epithelial cells is about 5 times the serum concentration [27]. This disproportionate accumulation of cisplatin in kidney tissue contributes to nephrotoxicity and proximal tubular cell damage [16, 28]. The degree of hypomagnesaemia noted in patients on cisplatin based chemotherapy has been related to the cisplatin cumulative dose [29]. It is noted that higher doses of cisplatin are associated with a higher degree of hypomagnesaemia and lower doses are associated with a lower degree of hypomagnesaemia. Renal toxicity with high dose cisplatin therapy (120mg/m2) was 36% and with moderate dose (60mg/m2) was 19% according to a study carried out in the USA [30]. Magnesium is not routinely measured in cancer patients on cisplatin based chemotherapy in many developing countries, though profound magnesium deficiency has several adverse effects on the body if it is unnoticed or if nothing is done about it. Hence, the aim of this study was to determine magnesium levels in cervical cancer patients who have completed 4 cycles of cisplatin based chemotherapy in at least 8 weeks.

2. MATERIALS AND METHODS

Study Design: Comparative longitudinal study over eight weeks of follow-up

Study Period: 2 November 2015 – 30 April 2016

Study Site: Parirenyatwa Group of Hospitals

Ethical Clearance: Permission to carry out the proposed research was sought from Joint Research Ethics Committee of College of Health Sciences and Parirenyatwa Group of Hospitals (JREC 362/15).

Study Participants: Study participants were cervical cancer patients on cisplatin based chemotherapy (older than 18 years)

Inclusion criteria: Cervical cancer patients on cisplatin based chemotherapy who received 4 cycles of cisplatin based chemotherapy over eight weeks.

Exclusion criteria: Cancer patients on non cisplatin based chemotherapy, on other drugs comprising

diuretics, aminoglycosides and cardiac glycosides which lead to hypomagnesaemia, renal disease and those deferred or did not complete their cisplatin cycle

Sample collection and storage: Serum was obtained from cervical cancer patients using venipuncture. Clotted blood samples were centrifuged and serum was separated, placed in serum pots and stored at -200C prior to thawing for analysis. Baseline samples were obtained at baseline before administration of cisplatin and follow up serum samples were collected after eight weeks of cisplatin exposure.

Sample analysis: Serum samples were thawed once at room temperature and analysis was done using the colorilmetric xylidyl blue dye complexing method on Mindray BS800 automated analyser. Calibration was carried out before analysis of samples and controls.

Classification of magnesium levels: The diagnosis of hypomagnesaemia was achieved using World Health Organisation reference ranges as follows: normal magnesium levels fall between 0.7mmo/L – 1.0mmol/L, hence serum levels less than 0.7mmol/L were used as a reference for hypomagnesaemia.

Hypomagnesaemia Grading: Severity of hypomagnesaemia was graded using the National Cancer Institute-Common Terminology Criteria for Adverse Events (CTCAE), as follows:

Grade 1	Mild	0.5-0.7mmol/L
Grade 2	Moderate	0.4-0.5mmol/L
Grade 3	Severe	0.3-0.4mmol/L
Grade 4	Life Threatening	<0.3mmol/L

Methods of Data analysis: Normally distributed variables were summarized using mean, standard deviation at a 95% confidence interval. Means were compared using student's t tests. The Statistical Package for Social Sciences (SPSS) Version 23 was used for data analysis.

3. RESULTS AND DISCUSSION

Female patients (N=82) were enrolled into the study, 51 (62.2%) were in Group 1 and 31 (37.8%) were in Group 2 and all patients had to be on cisplatin based chemotherapy for about eight weeks at follow-up. Mean age for Group 1 patients was 57.0±12.9 years and mean age for Group 2 was 55.2±12.5 years, p= 0.5371. Table 1 shows comparisons of the study participants by time of study and cisplastin dose. At baseline, 11% (n=9) of patients had mild hypomagnesaemia and mean magnesium levels were normal. At follow-up mean magnesium levels for both Groups 1 and 2 showed mild hypomagnesaemia and 60% of all patients had mild hypomagnesaemia. At follow-up, approximately 57% of Group 1 patients had mild hypomagnesaemia while 62% of patients in Group 2 had mild hypomagnesaemia (Table 1).

Table 1: Magnesium characteristics of study participants

Classification by cisplatin treatment dosages (N=82)			
Variables	**Group 1**	**Group 2**	**P value**
Chemotherapy dosage	50mg/m^2 cisplatin	75mg/m^2 cisplatin	
Number (%)	51 (62)	31 (38)	
Mean Mg$_{baseline}$	0.93 (0.25)	0.92 (0.02)	0.7764
Mean Mg$_{follow-up}$	0.68 (0.11)	0.64 (0.18)	0.1443
P value	<0.0001	<0.0001	
% change	-26.9	-30.4	
Classification by magnesium levels (N=82)			
	Normal magnesium Number (%)		**Hypomagnesinemia** Number (%)
Baseline	73 (89%)		9 (11%)
Follow-up	33 (40%)		49 (60%)
Group 1$_{follow-up}$	82 (43%)		47 (57%)
Group 2$_{follow-up}$	31 (38%)		51 (62%)

Group 1 study participants were on 50mg/m^2 Cisplatin based chemotherapy for at least 8 weeks (4 cycles of Cisplatin); Group 2 study participants were on 75mg/m^2 Cisplatin based chemotherapy for at least 8 weeks (4 cycles of Cisplatin), Normal magnesium range: 0.7mmo/L – 1.0mmol/L, Hypomagnesinemia: <0.7mmol/L

Table 1 also shows results for patients after completion of four cycles of cisplatin based chemotherapy. Patients in Group 1 showed a 27% decline in mean magnesium levels from 0.93±0.24mmol/L (baseline) to 0.68±0.11mmol/L while Group 2 patients showed a 30% decline in mean magnesium levels from 0.92±0.02mmol/L at baseline to 0.64±0.18mmol/L after eight weeks, $p<0.0001$, respectively. Figure 1 is an illustration of the changes in magnesium levels between baseline and follow-up for Group 1 and 2 patients.

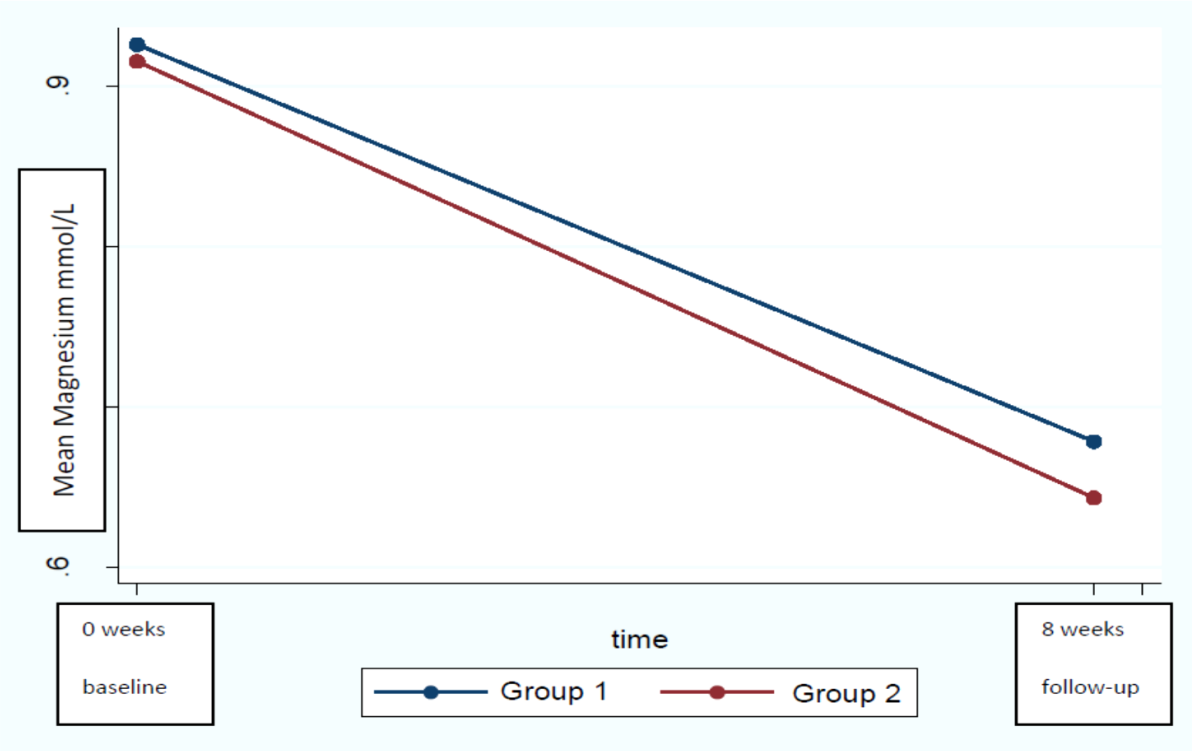

Table 1 shows mean magnesium levels at baseline for Group 1 and Group 2 were 0.93 ±0.24mmol/L and 0.92±0.02mmol/L, respectively and both were within the normal reference range. Approximately, 11% of all patients had mild hypomagnesaemia at baseline. The mild hypomagnesaemia at baseline was not cisplatin related as the patients had not yet started taking the drug and the hypomagnesaemia could have been due to other factors such as malnutrition or malarbsorption of magnesium [31]. Table 1 shows the results obtained after completion of the four cycles of cisplatin for at least eight weeks, Group 1 showed a 27% decline in mean magnesium levels from 0.93±0.24mmol/L (baseline) to 0.68±0.11mmol/L ($P<0.0001$), and the follow-up mean was mildly hypomagnesaemic. There are many reports of magnesium depletion using a usual dose or even a low dose of cisplatin and some cases show fatal results [32].Table 1 also shows results obtained after completion of the four cycles of cisplatin for Group 2 where there was a 30% decline in mean magnesium levels from 0.92±0.02mmol/L (baseline) to 0.64±0.18mmol/L ($P<0.0001$) and the follow-up mean showed mild hypomagnesaemia. In accordance with other studies, hypomagnesaemia is a known frequent complication of chemotherapy with cisplatin affecting 90% of patients [23]. There was no difference in mean magnesium levels between Group 1 and Group 2 patients at both time points ($P>0.0001$). Although it was not statistically significant, the incidence of hypomagnesaemia was slightly higher in Group 2 study participants. Both these findings should be validated by further studies on a larger population size to improve power of study and reduce type II error. This study confirms the findings of previous reports that indicate that hypomagnesaemia is a well known side effect of cisplatin based chemotherapy but did not confirm the inverse correlation between cumulative cisplatin dose and magnesium levels.

4. CONCLUSION

In conclusion, the present study does confirm that cisplatin based chemotherapy is associated with development of hypomagnesaemia after eight weeks of treatment. At baseline the magnesium levels were within normal ranges, on average, but declined to below normal at follow-up, suggesting association between development of hypomagnesaemia and cisplatin therapy. There was no significant difference in magnesium levels between patients on $50mg/m^2$ dose of cisplatin and $75mg/m^2$ cisplatin, at both time points, suggesting that hypomagnesaemia was not dose dependent in this study. Hence, the study did not confirm that higher doses of cisplatin are associated with greater loss of magnesium.

LIMITATIONS

Only cervical cancer patients were included in this study due to the fact that patients with other types of cancers were receiving different regimens that are not cisplatin. There were however a few patients with head and neck cancer that were receiving cisplatin but because their numbers were too low they were not included in the study. Perhaps confounding due to cancer type would have been accounted for if patients with other types of cancers had been included in the study. There were also fewer patients in Group 2 (receiving high dose of cisplastin) than those in Group 1 making comparison difficult. Time to follow-up could have been longer in order to ensure that the change in magnesium levels was not transient.

SUGGESTIONS AND RECOMMENDATIONS FOR FURTHER STUDY

Further studies involving other cancer types, studies with longer follow-up and larger population sizes are warranted to inform policy makers about whether there is need for magnesium to be routinely measured in cancer patients on cisplatin based chemotherapy at Parirenyatwa Group of Hospitals and in Zimbabwe in general.

CONFLICT OF INTEREST

There was no conflict of interest in this work

ACKNOWLEDGEMENTS

Staff and students of the Department of Medical Laboratory Sciences, University of Zimbabwe, College of Health Sciences

REFERENCES

1. D. Hanah, R.A. Weinberg. The Hallmarks of Cancer. Cell. 2000; (1): 57-100
2. S. Hodgson. Mechanisms of Cancer Susceptibility. Journal of Zhejiang University Science. 2008*;* 9(1): 1-4
3. F.P. Perera. Environment and cancer: Who are susceptible? Science. 2010; 278 (5340),1068-73
4. Weinberg, R.A. The Biology of Cancer. 796. 2006. Garland Science, New York.
5. N.E. Kushlinskiĭ and M.V. Nemtsova. Molecular Biological Characteristics of Cancer. Cancer. 2014; 10: 5-15.
6. H.C. Pitot and Y.P. Dragan. Facts and Theories Concerning the Mechanisms of Carcinogenesis. The Faseb Journal. 1991; 5: 2280-2286.
7. C.N Tenge. R.T. Kuremu, N.G. Buziba, K. Patel and P.A. Were. Burden and Pattern of Cancer in Western Kenya. East African Medical Journal. 2009; 86(1), 100-130
8. J. Ferlay, H. Shin, F.Bray, D. Frman, C. Mathers and D.M. Parkin. Cancer incidence and mortality worldwide. IARC cancer. 2008; 5: 20-25
9. E. Chokunonga, M.Z. Borok, Z.M. Chirenje, R. Makunike-Mutasa, N. Ndlovu, A.M Nyakabau and S.Vuma. Pattern of Cancer in Zimbabwe, Zimbabwe National Cancer Registry 2013 Annual Report. Zimbabwe. 2015; 1-59
10. Z.M. Chirenje, S. Rusakaniko, L. Kirumbi, EW. Ngwalle, P. Makuta-Tlebere, S. Kaggwa, W. M. Shumbusho, and L.Makoae. Situation Analysis for Cervical cancer diagnosis and Treatment in East central and Southern African Countries. Bulletin of the World Health Organization. 2001; 79 (2): 127-132
11. D.M. Parkin, P. Pisani and J. Ferlay. Estimates of the worldwide incidence of eighteen major cancers in 1985. International Journal of Cancer. 1993; 54: 594–606.
12. E. Chokunonga, M.Z. Borok, Z.M. Chirenje, R. Makunike-Mutasa and N. Ndlovu. Pattern of Cancer In Zimbabwe, Zimbabwe National Cancer Registry Annual Report. Harare, Zimbabwe National Cancer Registry. 1995; 6: 1-60
13. W.H. Kampala. D.M. Parkin. Cancer incidence in five continents, IARC Scientific Publication. 1997; 7:82-85
14. F.X. Bosch and S. de Sanjose. Human papillomavirus and cervical cancer - burden and assessment of causality, J Natl Cancer Inst Monogr. 2003; 31:3-13.
15. D.K. Shirley, R.J. Kaner, M.J. Glesby. Effects of Smoking on Non-AIDS-Related Morbidity in HIV-Infected Patients. Mayer KH, ed. Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America. 2013; 57(2): 275-282.
16. X. Yao, K. Panichpisal, N.Kurtzman, K.Nuggent. Cisplatin Nephrotoxicity: A Review, The American Journal of Medical Sciences. 2007; 334(2): 115-124

17. R.P. Miller, R.K. Tadagavadi, G. Ramesh and W.B.Reeves. Mechanisms of Cisplatin Nephrotoxicity. Toxins. . 2010; 2: 2490-2518
18. D. Chen, V. Milacic, M. Frezza and Q.P. Dou Metal complexes, their cellular targets and potential for cancer therapy. Curr. Pharm. Des. 2009; 15: 777–791.
19. B. Rosenberg, T.G. Spiro and E.J. Wiley In Nucleic Acid-Metal Ion Interactions. 1980. New York, NY, USA, 1–29.
20. B. Desoize and C. Madoulet. Particular aspects of platinum compounds used at present in cancer treatment; Crit Rev Oncol Hematol. 2002; 42: 317–325.
21. Z.H. Siddik. Cisplatin: mode of cytotoxic action and molecular basis of Resistance, Oncogene. 2003; 22: 7265–7279
22. K. Anvari, M.S. Toussi and M. Mirsadraee. Evaluation of Intravenous Magnesium Supplementation as Prophylaxis for Cisplatin-induced Hypomagnesemia, Middle East Journal of Cancer. 2010; 1(3): 109-114
23. R.L. Schilsky and T.O.M. Anderson. Hypomagnesemia and renal magnesium wasting in patients receiving cisplatin. Ann. Intern. Med. 1979; 90: 929–931.
24. F. Ries and J. Klastersky. Nephrotoxicity induced by cancer chemotherapy with special emphasis on cisplatin toxicity. Am. J. Kidney Dis. 1986; 13: 368–379
25. N. Shafaq and M. Tabassum. Effectiveness of carnosine on disturbed electrolytes homeostasis induced by cisplatin. Afr J Biotechnol. 2011; 10(37): 7286-7293
26. P. Arunkumar, G. Viswanatha, N. Radheshyam, H. Mukund and M. Belliyappa. Science behind cisplatin-induced nephrotoxicity in humans: A clinical study. Asian Pac J Trop Biomed. 2012; 2(8): 640-644
27. M.A. Mashhadi, Z. Heidari and Z. Zakeri. Mild Hypomagnesemia as the Most Common Cisplatin Nephropathy in Iran, Iranian Journal of Kidney Diseases. 2013; 7(1): 23-27
28. M.K. Kuhlmann, G. Burkhardt and H. Kohler. Insights into potential cellular mechanisms of cisplatin nephrotoxicity and their clinical application. Nephrol Dial Transplant. 1997; 12: 2478–80
29. I. Arany and R.L. Safirstein. Cisplatin nephrotoxicity. Semin Nephrol. 2003; 23: 460–4
30. K. Panichpisal, F.A. Pernett, S. Selhi and K.M. Nugent. Gitelman-like syndrome after cisplatin therapy: a case report and literature review, BMC Nephrol. 2006*;* 7: 10
31. F.N. Hutchison, E.A. Perez, D.R. Gandara, H.J. Lawrence and G.A. Kaysen. Renal salt wasting in patients treated with cisplatin, Ann Intern Med. 1988; 108: 21-5
32. H. Laje and, G. Daugaard. Cisplatin and hypomagnesemia, Cancer Treat Rev. 1999; 25(1): 47-58