of regorafenib therapy, which was observed in 91% of patients in this study. These therapy modifications were performed in 75.6% of the patients in the CORRECT study. The higher ratio of dose modification/interruption in the present study, than that in CORRECT study, might be due to several reasons. First, severe toxicities appeared more often in the present study. Any CTC-AE grades of fatigue and appetite loss were observed in 47% and 41% of the patients in this study, respectively, and grade 3 and higher fatigue and appetite loss were observed in 13% and 13%, respectively. Any grades and grade 3 of hand-foot skin reaction were also seen in 72% and 22%, respectively. Hand-foot skin reaction in this study occurred more frequently than that in the CORRECT study (any grades, 47%; grade 3, 17%). One possible explanation for this toxicity profile might be related to differences in ethnicity of the patient population when comparing the two studies. Since all dose modifications/interruptions during the therapy period were performed because of adverse events, more severe toxicities might lead to lower relative dose intensity. Second, 22% of patients were treated with a decreased dose of regorafenib during the initial cycle of treatment and liver dysfunction occurred in half of the patients. Most adverse events induced by regorafenib are ameliorated by therapeutic dose reduction and treatment delay, which underscores the dose-dependent nature of adverse events. Therefore, the initial dose reduction is inevitable, especially for patients who are at high risk of developing severe adverse events. While this strategy might result in decreased anti-tumor efficacy, outcomes were still good despite initial dose reduction. Four patients (13%) were given the planned dose of regorafenib for more than two cycles suggesting that initial dose reduction does not have a strong impact on efficacy.

OS and PFS were similar when comparing the present study to the CORRECT study, despite the lower relative dose intensity in the present study. The therapeutic dose reduction was performed mainly because of safety; improvements of quality of life (QOL) were not assessed in this study. Regorafenib monotherapy might help to maintain QOL by improving disease status (6). Therefore, salvage-line regorafenib monotherapy with dose reduction might improve survival while maintaining QOL.

Elevations in AST/ALT of grade 3 and higher were more frequently observed in the Japanese subpopulation than in the whole cohort in the CORRECT study (8), and a 62-year-old Asian man suffered grade 5 drug-induced liver dysfunction. In the present study, 19/16% patients had elevation in AST/ALT of grade 3 and higher and one patient died of liver dysfunction. A previous randomized phase III clinical trial of regorafenib monotherapy vs. placebo (GRID study) for advanced gastrointestinal stromal tumor demonstrated a survival benefit for regorafenib (7); one quarter of the enrolled patients in this study were Asians. A total of 98.5%

of patients in the regorafenib arm had adverse events (grade 3 and higher, 59.8%) and 68.2% of patients in the placebo arm had adverse events (grade 3 and higher, 9.1%). However, the incidence of liver dysfunction was not reported. The pharmacokinetic profiles of regorafenib and its active metabolites, M2 and M5, in a phase I study of Japanese solid tumor patients revealed that the range of regorafenib exposure was similar to those reported in European patients in phase I and II studies (9). These findings suggest that there is a high likelihood of developing liver dysfunction, especially in the Japanese population. Further study is needed to characterize the risk of regorafenib-induced liver dysfunction in Japanese and Asian populations.

Although the present study was a retrospective analysis of a small number of mCRC patients, we believe these data yield important insight into the efficacy adverse events of this therapy in a Japanese population. According to the present findings, uniform dose reduction and treatment delay could not be recommended but dose reduction, based on the toxicity profiles of each patient, should be actively considered. Exploration of biomarkers predicting the efficacy and safety of regorafenib and establishing safer treatment guidelines by clarifying the mechanism of regorafenib-induced liver dysfunction and other adverse events would be of benefit.

Acknowledgements

References

1 Haggar FA and Boushey RP: Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors. Clin Colon Rectal Surg 22: 191-197, 2009.
2 Matsuda A, Matsuda T, Shibata A, Katanoda K,. Sobue T, Nishimoto H and The Japan Cancer Surveillance Research Group: Cancer incidence and incidence rates in Japan in 2008: A study of 25 population-based cancer registries for the monitoring of cancer incidence in Japan (MCIJ) project. Jpn J Clin Oncol 44: 388-396, 2013.
3 Cutsem EV, Nordlinger B and Cervantes A: Advanced colorectal cancer: ESMO clinical practice guidelines for treatment. Ann Oncol 21(Suppl 2): v93-97, 2010.
4 Yamazaki K, Nagase M, Tamagawa H, Ueda S, Tamura T, Murata K, Tsuda T, Baba E, Tsuda M, Moriwaki T, Esaki T, Tsuji Y, Muro K, Taira K, Denda T, Tsushima T, Ando M, Morita S, Boku N, Hyodo I and West Japan Oncology Group: A randomized phase III trial of mFOLFOX6 plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment for metastatic colorectal cancer: West Japan Oncology Group study 4407G (WJOG4407G). J Clin Oncol 32: 5s, 2014 (suppl; abstr 3534).

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5 Wilhelm SM, Dumas J, Adnane L, Lynch M, Carter CA, Schütz G, Thierauch KH and Zopf D: Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. Int J Cancer 129: 245-255, 2011.

6 Grothey A, Cutsem EV, Sobrero A, Siena S, Falcone A, Ychou M, Humblet Y, Bouché O, Mineur L, Barone C, Adenis A, Tabernero J, Yoshino T, Lenz HJ, Goldberg RM, Sargent DJ, Cihon F, Cupit L, Wagner A, Laurent D for the CORRECT Study Group: Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet *381*: 303-312, 2013.

7 Demetri GD, Reichardt P, Kang YK, Blay JY, Rutkowski P, Gelderblom H, Hohenberger P, Leahy M, von Mehren M, Joensuu H, Badalamenti G, Blackstein M, Le Cesne A, Schöffski P, Maki RG, Bauer S, Nguyen BB, Xu J, Nishida T, Chung J, Kappeler C, Kuss I, Laurent D, Casali PG; GRID study investigators: Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet *381*: 295-302, 2013.

8 Yamada Y, Yoshino T, Komatsu Y, Yamazaki K, Tsuji A, Ura T, Grothey A, Cutsem EV, Wagner A and Ohtsu A: Safety and efficacy of regorafenib in Japanese patients with metastatic colorectal cancer: A subgroup analysis of the phase III CORRECT trial. Ann Oncol *24(Suppl 9)*: ix31-ix65, 2013.

9 Sunakawa Y, Furuse J, Okusaka T, Ikeda M, Nagashima F, Ueno H, Mitsunaga S, Hashizume K, Ito Y and Sasaki Y: Regorafenib in Japanese patients with solid tumors: phase I study of safety, efficacy, and pharmacokinetics. Invest New Drugs *32*: 104-112, 2014.

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Scientific
Research

Feasibility of Outpatient Chemotherapy with S-1 and Cisplatin for Gastric Cancer

Hironaga Satake, Akihito Tsuji, Takeshi Kotake, Mikio Fujita

Department of Oncology, Kobe City Medical Center General Hospital, Kobe, Japan
Email: hsatake@kcho.co.jp

Abstract

Objective: To evaluate the feasibility of S-1 and high-dose cisplatin short hydration regimens for outpatients with unresectable metastatic gastric cancer. Methods: Data for individual outpatients treated in our institution were retrospectively pooled to assess the feasibility of an S-1 and high-dose cisplatin short hydration regimen (S-1: 80 to 120 mg on Days 1 to 21; cisplatin: 60 mg/m^2 on Day 8, every 5 weeks), which included 2250 ml of intravenous fluids and 1000 ml oral hydration. Ten consecutive patients were treated with S-1 and high-dose cisplatin short hydration for unresectable metastatic gastric cancer from July 2011 to May 2012 and were included in the analysis. Results: With a median of 3.5 medication cycles, unscheduled admission occurred in two patients for 5 days each due to paralytic ileus and cerebral infarction. Four patients required dose reduction, in both S-1 and cisplatin in two patients, and in S-1 alone and cisplatin alone in one patient each. Renal function transiently declined after administration of cisplatin, but serum creatinine level and estimated glomerular filtration rate were both improved by the time of the next administration. Conclusion: This study suggests that an S-1 and high-dose cisplatin short hydration strategy for outpatients with unresectable metastatic gastric cancer might be feasible.

Keywords

Gastric Cancer, Cisplatin, S-1, Short Hydration, Outpatient Chemotherapy

1. Introduction

Gastric cancer is one of the most common causes of death in Japan. Standard treatment for unresectable metastatic gastric cancer consists of systemic chemotherapy, and the standard regimen consists of the platinum analogue cisplatin combined with 5-fluorouracil, particularly S-1. However, the administration of cisplatin is limited by nephrotoxicity, the dose-limiting toxicity of this agent. In Japan, to reduce nephrotoxicity, a 24-h hydration

period is recommended following administration. A number of trials have reported that hydration with 2 L and diuresis is sufficient to ensure the safety of cisplatin administration [1] [2], and that the addition of magnesium is effective in reducing this toxicity [3] [4]. From July 2011, we utilized an S-1 and high-dose cisplatin (SP) short hydration regimen based on the National Comprehensive Cancer Network (NCCN) Guidelines Template for patients with unresectable metastatic gastric cancer, and shifted administration from an inpatient to an outpatient basis. To our knowledge, only one report of outpatient chemotherapy with SP in patients with gastric cancer has been published in Asian, including Japan [5], however, the transition of renal function is unclear. Here, we retrospectively evaluated outpatient chemotherapy with SP short hydration for gastric cancer.

2. Materials and Methods

From July 2011 to May 2012, ten consecutive patients were treated with the SP short hydration regimen for metastatic gastric cancer at our institution underwritten informed consent. Data were retrospectively collected from medical charts, including past and present history; laboratory data for the evaluation of hepatic, renal, and bone marrow function; and physiological examinations. We also collected radiological examinations as follows: computed tomography (CT) of the chest, abdomen, and pelvis, and esophagogastroduodenoscopy (EGD) with biopsy to confirm histology.

All patients received oral (p.o.) administration of S-1 at a total daily dose of 80 - 120 mg, depending on body surface area, for 3 consecutive weeks, and a single intravenous (i.v.) administration of 60 mg/m^2 cisplatin on Day 8. On the day of cisplatin administration, patients also received 2250 ml hydration i.v. containing 5 mEq-total magnesium and 1000 ml hydration p.o. (Figure 1). Each cycle was followed by a 2-week rest period. Palonosetron 0.25 mg i.v., dexamethasone 20 mg i.v. and aprepitant 125 mg p.o. were administered 1 h before chemotherapy on Day 8. Aprepitant 80 mg p.o. and dexamethasone 4 mg p.o. were administered on Days 2 and 3. S-1 dose was calculated according to patient body surface area as follows: less than 1.25 m^2, 40 mg; 1.25 - 1.5 m^2, 50 mg; and greater than 1.5 m^2, 60 mg. Treatment was continued until one of the following occurred: progressive disease, unacceptable toxicity, patient refusal, or termination of treatment by the attending physician. Follow-up was conducted every one to four weeks. Each follow-up included a physical examination and blood study. A CT scan was conducted every four to six weeks. Adverse events were graded according to the National Cancer Institute Common Toxicity criteria (CTCAE; version 3.0). Renal function was assessed based on serum creatinine (SCr) level and estimated glomerular filtration rate (eGFR) by blood examination every week during
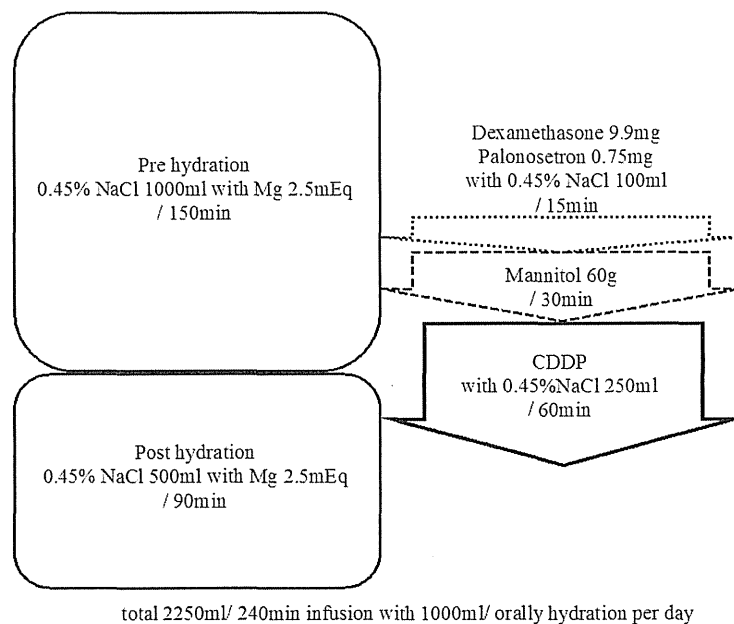

total 2250ml/ 240min infusion with 1000ml/ orally hydration per day

Figure 1. Cisplatin administration. NaCl, sodium chloride; Mg, magnesium; min, minutes; CDDP, cisplatin.

the 1st cycle, and before administration of cisplatin on Day 8 in every course from the 2nd cycle. The study was approved by the Institutional Review Board of our institution.

3. Results

3.1. Baseline Characteristics

Baseline characteristics are listed in Table 1. Disease status was unresectable in seven patients and post-operative recurrence in three. The site of metastasis was the liver in two cases and the testis in one. Two patients had received previous adjuvant chemotherapy with S-1.

3.2. Treatment Compliance and Continuation

Treatment compliance and response are summarized in Table 2. The median number of medication cycles was 3.5. Unscheduled admission occurred in two patients, both for 5 days, due to paralytic ileus and cerebral infarction in one patient each. Both were treated with conservative therapies. The patient with cerebral infarction had a history of previous cerebral infarction. Lacunar infarction was discovered following the onset of transient aphasia on Day 15 from the start of the 2nd SP short hydration course, and was treated with anticoagulant agent warfarin potassium. The patient with paralytic ileus was a post-operative case who had a history of paralytic ileus

Table 1. Baseline characteristics.

Characteristic		n = 10
Age (yr)	Median (range)	66.5 (56 - 76)
Gender	Male/Female	8/2
ECOG PS	0/1	8/2
Surgery	Unresectable/Recurrence	7/3
HER2 status	Positive/Negative/Unknown	2/6/2
Metastatic site	0/1	7/3
Peritoneal dissemination	Present	4
Pre-chemotherapy	Adjuvant S-1	2

ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor type 2.

Table 2. Treatment compliance and response.

	n = 10
Total chemotherapy cycle, median (range)	3.5 (1 - 9)
Unexpected administration, n (%)	2 (20)
Days, mean (range)	5 days (5)
Reason	Paralytic ileus Cerebral infarction
Dose reduction, n (%)	4 (40)
S-1, CDDP	2 (20)
S-1 alone	1 (10)
CDDP alone	1 (10)
Extension, n (%)	1 (10)
Reason	Leukopenia
Interruption, n (%)	4 (40)
Reason	PD 1 AE 3

CDDP, cisplatin; PD, progressive disease; AE, adverse event.

after a previous operation. The paralytic ileus was improved with conservative treatment.

Four patients required a dose reduction, as follows: reduction in both S-1 and cisplatin due to Grade 2 neutropenia and Grade 2 fatigue (n = 2); reduction in S-1 alone due to Grade 3 anemia (n = 1); and reduction in cisplatin alone due to Grade 2 appetite loss (n = 1). Treatment was extended in one patient due to Grade 3 leukopenia, and interrupted in four patients due to progressive disease (n = 1), and adverse events, including diarrhea (n = 1), cerebral infarction (n = 1) and peripheral sensory neuropathy (n = 1).

3.3. Toxicity

Acute toxicities are listed in Table 3 and Table 4. Acute Grade 3 or 4 hematologic toxicity included leukopenia in 10% (1/10), neutropenia in 10% (1/10) and anemia in 30%. Acute Grade 3 or 4 non-hematologic toxicity included anorexia in 10% (1/10), paralytic ileus in 10% (1/10) and cerebral infarction in 10% (1/10). There were no cases of vomiting of any grade and no treatment-related deaths. Changes in serum creatinine (SCr) and estimated glomerular filtration rate (eGFR) are shown in Figure 2 and Table 5. Renal function transiently declined after administration of cisplatin. However, SCr and eGFR were improved by the time of the next administration.

4. Discussion

In this study, we observed that renal function transiently declined following the administration of cisplatin, but improved by the time of the next administration. The incidence of Grade 3 or 4 adverse events was 10% - 30%

Table 3. Hematological toxicities during chemotherapy (n = 10).

Adverse Event	NCI-CTC Grade				
	1	2	3	4	3/4 (%)
Leukopenia	2	2	1	0	10
Neutropenia	2	3	1	0	10
Anemia	1	2	3	0	30
Thrombocytopenia	1	1	0	0	0
Creatinine	2	0	0	0	0

Table 4. Non-hematological toxicities during chemotherapy (n = 10).

Adverse event	NCI-CTC Grade				
	1	2	3	4	3/4 (%)
Anorexia	3	3	1	0	10
Cerebral infarction	0	0	1	0	10
Constipation	2	1	0	0	0
Diarrhea	1	3	0	0	0
Dysgeusia	1	0	0	0	0
Fatigue	4	3	0	0	0
Fever	1	0	0	0	0
Hiccups	1	0	0	0	0
Mucositis oral	0	2	0	0	0
Nausea	2	2	0	0	0
Paralytic ileus	0	0	1	0	10
Peripheral sensory neuropathy	0	1	0	0	0
Pruritus	1	0	0	0	0
Rash	1	0	0	0	0
Vomiting	0	0	0	0	0

Table 5. Transition of serum creatinine (SCr) and estimated glomerular filtration rate (eGFR).

	SCr (mg/dl)	eGFR (mL/min)
	Mean ± SE	Mean ± SE
Cycle 1 Day 8	0.69 ± 0.15	87.8 ± 12.4
Cycle 1 Day 15	0.93 ± 0.24	72.5 ± 15.6
Cycle 1 Day 22	0.74 ± 0.12	76.2 ± 16.0
Cycle 2 Day 8	0.82 ± 0.22	74.6 ± 16.6
Cycle 3 Day 8	0.84 ± 0.24	76.3 ± 15.7
Cycle 4 Day 8	0.79 ± 0.27	83.8 ± 15.8
Cycle 5 Day 8	0.85 ± 0.24	67.3 ± 13.5
Cycle 6 Day 8	0.83 ± 0.23	69.5 ± 16.3
Cycle 7 Day 8	0.92 ± 0.32	68.0 ± 19.1
Cycle 8 Day 8	0.96 ± 0.33	66.5 ± 23.3

SCr, serum creatinine; eGFR, estimated glomerular filtration rate; SE, standard error.
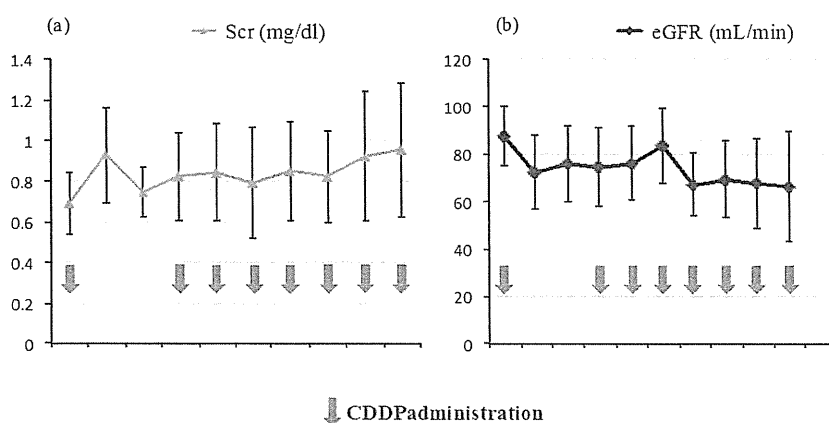

Figure 2. Changes in of serum creatinine level and estimated glomerular filtration rate (n = 10). (a) Change in serum creatinine; (b) Change in estimated glomerular filtration rate.

for myelosuppression, 10% for anorexia, 10% for paralytic ileus and 10% for cerebral infarction. In the SPIRITS trial, a cornerstone Phase III trial of S-1 plus cisplatin for metastatic gastric cancer, Grade 3 or 4 adverse events in the SP arm were as follows: leucopenia (11%), neutropenia (40%), anemia (26%), thrombocytopenia (5%), febrile neutropenia (3%), anorexia (30%), nausea (11%), fatigue (4%), vomiting (4%), diarrhea (4%), stomatitis (0.7%), rash (2%) and hyponatremia (3%) [6]. Allowing for the substantial limitations of our study, these results are considered comparable with the previous study.

The optimal intravenous solution and regimen for hydration are unclear, but in general at least 2 L of i.v. saline is required on the day of cisplatin administration to maintain good urine flow. This was therefore only conducted on the day of cisplatin administration. In Italy, Tiseo *et al.* (2007) also reported that a short period of hydration, including 2000 ml of fluid with control of diuresis, is feasible [7]. One reason for hydration is the critical importance of maintaining urine flow within 4 - 6 h of cisplatin administration to prevent nephrotoxicity. Approximately 90% of platinum becomes irreversibly bound to plasma protein within 4 h after cisplatin administration, and the plasma concentration of free platinum, which induces nephrotoxicity, decreases almost to the limit of quantification within 4 - 6 h after administration [8]. Most countries have accordingly started to administer cisplatin on an outpatient basis, but this change has yet to occur in Japan [9]. The development of the antiemetic drug aprepitant, a potent and selective antagonist of the neurokinin (NK)1 neurotransmitter receptor, and palonosetron, a second generation 5-hydroxytryptamine 3 (5-HT(3))-receptor antagonist, prevent chemotherapy-

induced nausea and vomiting (CINV)] [10]-[12]. In our study, we administered aprepitant, palonosetron and dexamethasone to prevent CINV, and Grade 3 or 4 nausea was not observed. This in turn allowed the oral intake of food and water, and acceptable nephrotoxicity.

In economic terms, inpatient chemotherapy with a high-dose cisplatin regimen usually requires at least three days of administration, giving a medical cost in Japan of at least US $1200 for every cycle. In contrast, outpatient chemotherapy with high-dose cisplatin in combination with aprepitant plus palonosetron and dexamethasone as antiemetic prophylaxis costs approximately $700 per cycle in Japan. Total administration time of each SP short hydration regimen, which included 2250 ml of fluids with diuresis, was approximately 4 hours, allowing the management of the same regimen twice per day in the outpatient department.

Limitations of the study include its small number of patients and single institution, retrospective study design.

This study suggests that the SP short hydration strategy might be feasible in Japanese patients with gastric cancer, and can provide time saving for patients and reduce medical costs. A Phase II study of S-1 and high-dose cisplatin chemotherapy with short hydration for unresectable metastatic gastric cancer is now ongoing as part of the Japan Southwest Research Support Organization Group trial (JWOG-G1 trial).

References

[1] Stewart, D.J., Dulberg, C.S., Mikhael, N.Z., Redmond, M.D., Montpetit, V.A. and Goel, R. (1997) Association of Cisplatin Nephrotoxicity with Patient Characteristics and Cisplatin Administration Methods. *Cancer Chemotherapy and Pharmacology*, 40, 293-308. http://dx.doi.org/10.1007/s002800050661

[2] Vogl, S.E., Zaravinos, T. and Kaplan, B.H. (1980) Toxicity of Cis-Diamminedichloroplatinum II Given in a Two-Hour Outpatient Regimen of Diuresis and Hydration. *Cancer*, 45, 11-15. http://dx.doi.org/10.1002/1097-0142(19800101)45:1<11::AID-CNCR2820450104>3.0.CO;2-E

[3] Willox, J.C., McAllister, E.J., Sangster, G. and Kaye, S.B. (1986) Effects of Magnesium Supplementation in Testicular Cancer Patients Receiving Cis-Platin: A Randomised Trial. *British Journal of Cancer*, 54, 19-23. http://dx.doi.org/10.1038/bjc.1986.147

[4] Bodnar, L., Wcislo, G., Gasowska-Bodnar, A., Synowiec, A., Szarlej-Wcislo, K. and Szczylik, C. (2008) Renal Protection with Magnesium Subcarbonate and Magnesium Sulphate in Patients with Epithelial Ovarian Cancer after Cisplatin and Paclitaxel Chemotherapy: A Randomised Phase II Study. *European Journal of Cancer*, 44, 2608-2614. http://dx.doi.org/10.1016/j.ejca.2008.08.005

[5] Okazaki, S., Nakajima, T.E., Hashimoto, J., Yamamoto, S., Takahari, D., Kato, K., Hamaguchi, T., Yamada, Y., Shimada, Y. and Tamura, K. (2013) A Feasibility Study of Outpatient Chemotherapy with s-1 + Cisplatin in Patients with Advanced Gastric Cancer. *Gastric Cancer*, 16, 41-47. http://dx.doi.org/10.1007/s10120-012-0139-4

[6] Koizumi, W., Narahara, H., Hara, T., Takagane, A., Akiya, T., Takagi, M., Miyashita, K., Nishizaki, T., Kobayashi, O., Takiyama, W., Toh, Y., Nagaie, T., Takagi, S., Yamamura, Y., Yanaoka, K., Orita, H. and Takeuchi, M. (2008) S-1 plus Cisplatin versus s-1 Alone for First-Line Treatment of Advanced Gastric Cancer (Spirits Trial): A Phase III Trial. *The Lancet Oncology*, 9, 215-221. http://dx.doi.org/10.1016/S1470-2045(08)70035-4

[7] Tiseo, M., Martelli, O., Mancuso, A., Sormani, M.P., Bruzzi, P., Di Salvia, R., De Marinis, F. and Ardizzoni, A. (2007) Short Hydration Regimen and Nephrotoxicity of Intermediate to High-Dose Cisplatin-Based Chemotherapy for Outpatient Treatment in Lung Cancer and Mesothelioma. *Tumori*, 93, 138-144.

[8] Sasaki, Y., Tamura, T., Eguchi, K., Shinkai, T., Fujiwara, Y., Fukuda, M., Ohe, Y., Bungo, M., Horichi, N., Niimi, S., Minato, K. and Nakagawa, K. (1989) Pharmacokinetics of (Glycolate-0,0')-Diammine Platinum (II), a New Platinum Derivative, in Comparison with Cisplatin and Carboplatin. *Cancer Chemotherapy and Pharmacology*, 23, 243-246. http://dx.doi.org/10.1007/BF00451649

[9] Yamada, K., Yoshida, T., Zaizen, Y., Okayama, Y., Naito, Y., Yamashita, F., Takeoka, H., Mizoguchi, Y. and Azuma, K. (2011) Clinical Practice in Management of Hydration for Lung Cancer Patients Receiving Cisplatin-Based Chemotherapy in Japan: A Questionnaire Survey. *Japanese Journal of Clinical Oncology*, 41, 1308-1311. http://dx.doi.org/10.1093/jjco/hyr145

[10] Longo, F., Mansueto, G., Lapadula, V., Stumbo, L., Del Bene, G., Adua, D., De Filippis, L., Bonizzoni, E. and Quadrini, S. (2012) Combination of Aprepitant, Palonosetron and Dexamethasone as Antiemetic Prophylaxis in Lung Cancer Patients Receiving Multiple Cycles of Cisplatin-Based Chemotherapy. *International Journal of Clinical Practice*, 66, 753-757. http://dx.doi.org/10.1111/j.1742-1241.2012.02969.x

[11] Rapoport, B.L., Jordan, K., Boice, J.A., Taylor, A., Brown, C., Hardwick, J.S., Carides, A., Webb, T. and Schmoll, H.J. (2010) Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting Associated with a Broad Range of Moderately Emetogenic Chemotherapies and Tumor Types: A Randomized, Double-Blind Study. *Support Care Cancer*, 18, 423-431. http://dx.doi.org/10.1007/s00520-009-0680-9

[12] Saito, M., Aogi, K., Sekine, I., Yoshizawa, H., Yanagita, Y., Sakai, H., Inoue, K., Kitagawa, C., Ogura, T. and Mitsu-hashi, S. (2009) Palonosetron plus Dexamethasone versus Granisetron plus Dexamethasone for Prevention of Nausea and Vomiting during Chemotherapy: A Double-Blind, Double-Dummy, Randomised, Comparative Phase III Trial. *The Lancet Oncology*, **10**, 115-124. http://dx.doi.org/10.1016/S1470-2045(08)70313-9

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