Methotrexate and Leucovorin Double-modulated 5-Fluorouracil Combined with Cisplatin (MPFL) in Metastatic/Recurrent Head and Neck Cancer

Peter Mu-Hsin Chang[1,3], Hao-Wei Teng[1,3], Po-Min Chen[1,3], Shyue-Yih Chang[2], Pen-Yuan Chu[2], Tung-Lung Tsai[2], Shyh-Kuan Tai[2], Yi-Fen Wang[2], Jui-Lin Huang[2], Muh-Hwa Yang[1,3]*

[1]Division of Medical Oncology, Department of Medicine, and [2]Department of Otolaryngology, Taipei Veterans General Hospital, and [3]National Yang-Ming University School of Medicine, Taipei, Taiwan, R.O.C.

Background: To determine the efficacy and safety profile of the combination of cisplatin and 5-fluorouracil modulated both by methotrexate and leucovorin in metastatic/recurrent squamous cell carcinoma of the head and neck.

Methods: Twenty-eight patients were treated with cisplatin 40 mg/m^2/day continuous infusion for 24 hours on day 1; high-dose 5-fluorouracil 2,000 mg/m^2/day and leucovorin 100 mg/m^2/day continuous infusion for 48 hours on days 1 and 2; methotrexate 40 mg/m^2/day as a bolus infusion 4 hours before 5-fluorouracil and leucovorin on day 1. The treatment was repeated every 2 weeks in a cycle.

Results: The overall response rate was 25%, and 14% of the patients achieved stable disease status. Subgroup analysis demonstrated significantly improved overall survival in the disease-control group (12.0 months *vs*. 5.3 months, $p < 0.001$). Only 3 (10.7%) patients developed grade 3–4 neutropenia, and none developed grade 3–4 non-hematologic toxicity.

Conclusion: This multiagent-containing regimen has an excellent safety profile and improved survival in disease-control group of patients with metastatic/recurrent squamous cell carcinoma of the head and neck. [*J Chin Med Assoc* 2008; 71(7):336–341]

Key Words: cisplatin, fluorouracil, head and neck cancer, methotrexate, mucositis

Introduction

Carcinomas of the head and neck, including cancers originating from the oral cavity, oropharynx, hypopharynx and larynx, represent the sixth most frequent type of cancer in the world. The most common type of head and neck cancer is squamous cell carcinoma (HNSCC), which accounts for more than 90% of oral malignancies.[1] The main etiologic factors in the West include alcohol consumption, tobacco use, and poor oral hygiene; whereas in Asia it is commonly linked to the habit of betel nut chewing (e.g. in Taiwan).[2–4] The management of metastatic/recurrent HNSCC remains a major obstacle for medical oncologists and surgeons because of its treatment resistance and poor prognosis despite major technological advances in HNSCC treatment in recent years.[1,5]

A number of chemotherapeutic agents have activity against HNSCC, including methotrexate, cisplatin, bleomycin, 5-fluorouracil (5-FU), docetaxel, and paclitaxel. To date, cisplatin has been associated with increased survival versus supportive care.[6] Cisplatin/5-FU combination therapy is the most common treatment for patients with unresectable and recurrent HNSCC after radical surgery or radiotherapy. However, conventional cisplatin/5-FU chemotherapy is associated with significant dose-limiting grade 3–4 mucositis and prolonged administration time, which are problematic in this patient population.[7]

Weekly high-dose 5-FU (2,000–2,600 mg/m^2/day, continuous infusion for 24 hours, per 1 week) has been shown to have a relatively lower non-hematologic toxicity compared with traditionally administrated 5-FU in other cancers.[8–14] To eliminate the dose-limiting

*Correspondence to: Dr Muh-Hwa Yang, Division of Medical Oncology, Department of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, R.O.C.
E-mail: mhyang2@vghtpe.gov.tw • Received: December 17, 2007 • Accepted: May 23, 2008

toxicity of the conventional cisplatin/5-FU regimen (5-FU: 1,000 mg/m^2/day, continuous infusion for 96 hours, per 3 weeks) used in metastatic/recurrent HNSCC, we changed the conventional 5-FU regimen to biweekly high-dose 5-FU (2,000 mg/m^2/day, continuous infusion for 48 hours, per 2 weeks). In addition, both methotrexate and leucovorin have been reported to have a chemomodulating effect on 5-FU.[15–18] We therefore designed a regimen that combined cisplatin with biweekly high-dose 5-FU modulated by both methotrexate and leucovorin (MPFL) to decrease toxicity and maximize the effect of high-dose 5-FU in metastatic/recurrent HNSCC patients.

Methods

Patient eligibility

From September 2001 to December 2003, patients with recurrent/metastatic squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, and larynx in Taipei Veterans General Hospital, Taiwan, were enrolled in this study. The protocol was approved by the institutional review board. The eligibility criteria were distant metastasis or locoregional recurrent HNSCC (unresectable and unsuitable for radiotherapy). The inclusion criteria were: radiologically assessable disease; life expectancy > 3 months; Eastern Cooperative Group performance status ≤ 2; adequate hematologic, renal, and liver function; and signed informed consent. The exclusion criteria were: brain metastasis proven by computed tomography (CT); significant comorbidities with major organ dysfunction; other malignancy except basal cell skin carcinoma or cervical carcinoma *in situ*.

Treatment scheme

After vigorous hydration, urinary alkalinization, and administration of antiemetics, patients were treated with cisplatin 40 mg/m^2/day continuous infusion for 24 hours on day 1; high-dose 5-FU 2,000 mg/m^2/day and leucovorin 100 mg/m^2/day continuous infusion for 48 hours on days 1 and 2; methotrexate 40 mg/m^2/day bolus infusion for 4 hours before 5-FU on day 1. The treatment was repeated every 2 weeks in a cycle.

Evaluation of treatment response

Before initiation of chemotherapy, patients were evaluated with a complete history and physical examination, performance status recording, complete blood cell count, and serum biochemistries. CT was performed to evaluate target lesions. Other examinations were performed only in the presence of a clinical indication. Laboratory tests were repeated before the start of each cycle. Evaluation for tumor response was performed every 3 months with CT scan. Tumor response was defined according to RECIST (Response Evaluation Criteria In Solid Tumors) criteria.[19]

Evaluation of toxicity and dose adjustment

Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0 and were evaluated before each treatment cycle. Treatment was withheld for 1 week if neutrophil count was < 1,500/mL and platelet count was < 75,000/mL at the time of chemotherapy recycling. If full hematologic recovery did not occur within 2 weeks, the treatment was discontinued. If grade 4 hematologic toxicity occurred, the protocol required a reduction to 75% of the planned dose in subsequent courses, even after full recovery. Granulocyte colony-stimulating factor was not given prophylactically but was permitted in patients with grade 3–4 neutropenia. Cisplatin dose was reduced by 50% when creatinine clearance (CCr) was 40–60 mL/min, and was withheld when CCr was < 40 mL/min. If grade 3 or 4 mucositis developed, the dose of methotrexate and 5-FU was reduced by 25% in the subsequent cycle.

Statistical analysis

SPSS version 13 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Kaplan-Meier estimate was used for survival analysis, and log-rank test was used for comparison between group overall survival rates. The response analysis of each clinical factor was compared using the χ^2 test (for expected values > 5) or Fisher's exact test (for expected values ≤ 5) for categorical variables. The level of statistical significance was set at a 2-sided p value < 0.05 for all tests.

Results

Patient characteristics and treatment response

From September 2001 to December 2003, 28 patients (26 men, 2 women) were enrolled in the study. Among the study population, 11 patients had primary metastatic disease without any treatment before diagnosis and 17 patients had locoregional recurrence after initial surgical resection followed by postoperative concurrent chemoradiation (CCRT). The median follow-up period was 15 months, and the median number of treatment cycles was 4 (range, 2–9). The median age of the patients was 52 years (range, 34–76 years). The patient characteristics are listed in Table 1.

Regarding treatment response, there was no complete response. Seven (25%) patients had a partial

response (PR), whereas 4 (14%) achieved stable disease (SD). The overall response rate and disease control rate (defined as complete response [CR] + PR + SD) were 25% and 39%, respectively. No significant correlation could be demonstrated between the clinical factors (primary sites, metastatic sites, age, sex, types of previous treatment) and treatment response (data not shown).

Table 1. Characteristics of the 28 patients

Age, yr	
Range	34–76
Median	52
Sex, *n*	
Male	26
Female	2
Primary tumor site, *n*	
Hypopharynx	17
Larynx	4
Oral cavity	2
Oropharynx	5
Performance status (ECOG), *n*	
0–1	12
2	16
Disease status, *n*	
Distant metastasis	11
Lung	7
Liver	3
Bone	1
Locoregional recurrence	17

ECOG = Eastern Cooperative Oncology Group.

Survival analysis

The Kaplan-Meier estimated overall survival curve for the 28 patients is shown in Figure 1A. The median survival for all patients was 7.9 months, which was similar to other reports (6-month median survival time in most studies conducted in the last 20 years).[5,20–23] To evaluate the effect of disease controlled by MPFL on overall survival, survival analysis using the log-rank test was performed in patients grouped as the disease-control group ($n = 11$) and disease-progression group ($n = 17$). Significantly improved survival rate was demonstrated in the disease-control group (Figure 1B). The median survival periods of the disease-control and disease-progression groups were 12.0 months and 5.3 months ($p < 0.001$), respectively.

Adverse events

The treatment-related toxicity of MPFL in all patients is shown in Table 2. Only 3 (10.7%) patients developed grade 3–4 neutropenia, whereas no grade 3–4 nonhematologic toxicity was identified. A low incidence of mucositis was noted.

Discussion

Despite advances in the treatment of patients with HNSCC, recurrent/metastatic HNSCC carries a poor prognosis, with a median overall survival of around 5.0–8.2 months.[5,7,20–23] Till now, the survival benefit of chemotherapy for recurrent/metastatic HNSCC is still unsatisfactory, with a 1-year survival rate of around 40%.[7] For more than a decade, the most common

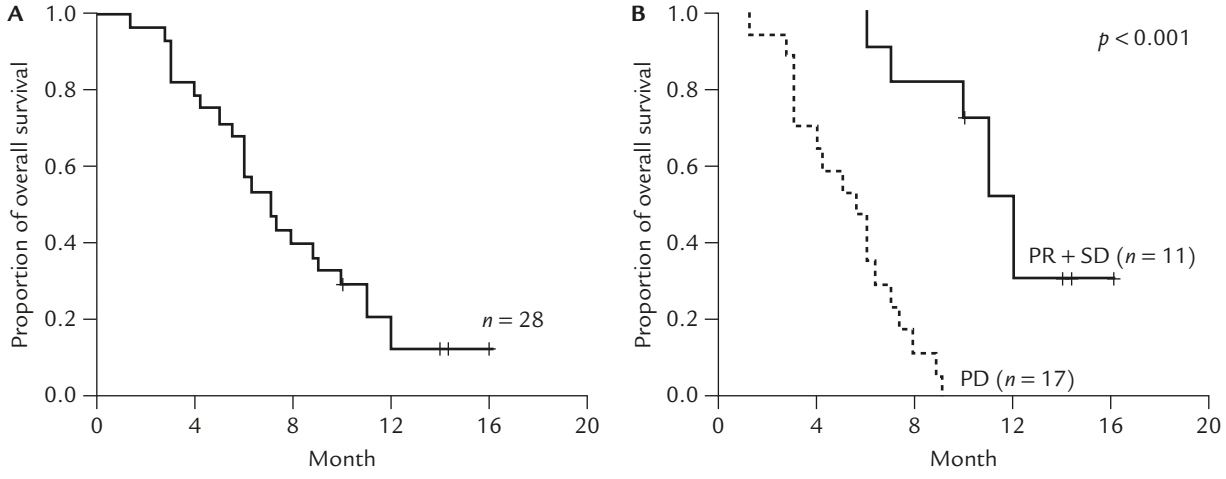

Figure 1. Kaplan-Meier plots: (A) overall survival; (B) overall survival related to treatment response. PR = partial remission; SD = stable disease; PD = progressive disease.

Table 2. Adverse events in the 28 patients*

Toxicity	NCI-CTC grade			
	1	2	3	4
Hematologic				
Anemia	5 (17.9)	3 (10.7)	0 (0)	0 (0)
Neutropenia	8 (28.6)	3 (10.7)	3 (10.7)	0 (0)
Thrombocytopenia	4 (14.3)	1 (3.6)	0 (0)	0 (0)
Infection	1 (3.6)	0 (0)	0 (0)	0 (0)
Renal	2 (7.1)	2 (7.1)	0 (0)	0 (0)
Liver	1 (3.6)	0 (0)	0 (0)	0 (0)
Mucositis	5 (17.9)	2 (7.1)	0 (0)	0 (0)
Nausea/vomiting	4 (14.3)	2 (7.1)	0 (0)	0 (0)
Diarrhea	5 (17.9)	0 (0)	0 (0)	0 (0)
Cutaneous	3 (10.7)	0 (0)	0 (0)	0 (0)

**Data presented as n (%). NCI-CTC = National Cancer Institute Common Toxicity Criteria (version 2.0).*

Table 3. Median survival, response rate, grade 3–4 neutropenia and mucositis in selected trials, including our MPFL regimen

5-FU schedule	Median survival (mo)	Response rate (%)	Grade 3–4 neutropenia (%)	Grade 3–4 mucositis (%)	References
Non head & neck neoplasm					
Weekly HD 5-FU*	–	–	0–34	0–5.9	8, 10, 12, 13, 24
Head & neck neoplasm					
NPC					
Weekly HD 5-FU*	–	–	0	0	9
Non-NPC					
Conventional 5-FU†/cisplatin	5.5–8.7	25–47.1	8.2–67	6–31	5, 20, 21, 22, 23
Biweekly HD 5-FU‡/cisplatin (MPFL§)	7.9	25	10.7	0	

**More than 2,000 mg/m^2/day, continuous infusion 1 day weekly; †1,000 mg/m^2/day, continuous infusion for 96 hours per 3 weeks; ‡more than 2,000 mg/m^2/day, continuous infusion 2 days biweekly; §combination of cisplatin and biweekly high-dose 5-FU modulated by methotrexate and leucovorin. 5-FU = 5-fluorouracil; HD = high-dose; NPC = nasopharyngeal carcinoma.*

chemotherapy for recurrent/metastatic HNSCC has been the conventional cisplatin/5-FU regimen.[5,7,18,20–23] However, the dose-limiting toxicity has a negative impact on the quality of life of advanced HNSCC cases. Newer treatment protocols should be developed to decrease the toxicity and improve the quality of life of HNSCC patients without compromising the effectiveness of treatment (e.g. treatment response, survival). We therefore designed the MPFL regimen in order to test its effectiveness and tolerability in advanced HNSCC.

The most important observation with regard to our MPFL regimen was the lower grade 3–4 mucositis (0%). Mucositis is the major dose-limiting non-hematologic toxicity of the conventional 5-FU schedule, with the incidence of grade 3–4 toxicity ranging from 6% to 31% (Table 3).[5,8–10,12,13,20–24] This adverse event may be related to the longer duration of 5-FU continuous infusion. In the previous studies of other cancers shown in Table 3, the rate of grade 3–4 mucositis was lower in high-dose 5-FU groups than in conventional 5-FU groups (0–5.9% *vs.* 6–31%). The reason for the lower mucositis rate is possibly that the administration of biweekly high-dose infusional 5-FU permits phosphatase recovery or activation in mucosa cells. In a previous animal study, 5-FU alone inhibited the activity of several enzymes, including thymidine-kinase, maltase and alkaline-phosphatase. The nadir of enzyme activity was between 24 and 96 hours after 5-FU administration, and complete regeneration took a week.[25] It is known that adequate phosphatase activity to metabolize FdUMP is a common mechanism for mucosa cell recovery. This result might contribute to better life quality.

Methotrexate alone has also been used in the past because of its low dose-limiting toxicity, but lower response rate has restricted its clinical application. Forastiere et al reported that the response rate to

methotrexate alone was 10% and the rate of grade 3–4 mucositis was 10%.[20] Other new-generation chemotherapeutic agents, such as taxanes, have recently been used in the management of recurrent/metastatic HNSCC, and no grade 3–4 mucositis was noted. However, the high incidence of grade 3–4 hematologic toxicity and low cost-effectiveness has limited its clinical application. Gibson et al reported a 26% response rate in patients treated with a combination of paclitaxel and cisplatin; 55% of paclitaxel/cisplatin-treated patients developed grade 3–4 neutropenia, and 4% of patients died of infection.[21]

In our study, the therapeutic effect of the MPFL regimen for metastatic/recurrent HNSCC was not superior to those of previous studies, with a modest response rate of 25% and median survival of 7.9 months.[5,20–23] There was also some disadvantage in that the continuous parenteral administration of cisplatin and 5-FU require that patients be hospitalized for at least 3 days. However, the toxicity profile suggested that the regimen was well tolerated. Only 3 (10.7%) patients had grade 3 neutropenia, none had grade 4 neutropenia or grade 3–4 non-hematologic toxicities, none had severe treatment-related morbidity, and none died because of the treatment.

In conclusion, our results demonstrated that the MPFL regimen has better tolerability without compromising treatment effectiveness (e.g. treatment response, survival) compared with previous reports, and the survival benefit was observed in the disease-control group. This indicates that the MPFL regimen should be considered for late-stage HNSCC cases as it is better tolerated and its effectiveness is comparable to other regimens. We suggest that new multiagent protocols be studied for effectiveness on survival and quality of life.

Acknowledgments

This work was supported by grants from the Taiwan Clinical Oncology Research Foundation.

References

1. Hardisson D. Molecular pathogenesis of head and neck squamous cell carcinoma. *Eur Arch Otorhinolaryngol* 2003;260:502–8.
2. Chen CL, Chi CW, Liu TY. Hydroxyl radical formation and oxidative DNA damage induced by areca quid *in vivo*. *J Toxicol Environ Health A* 2002;65:327–36.
3. Ko YC, Huang YL, Lee CH, Chen MJ, Lin LM, Tsai CC. Betel quid chewing, cigarette smoking and alcohol consumption related to oral cancer in Taiwan. *J Oral Pathol Med* 1995; 24:450–3.
4. Lin SC, Wang CP, Chen YM, Lu SY, Fann MJ, Liu CJ, Kao SY, et al. Regulation of IGFBP-5 expression during tumorigenesis and differentiation of oral keratinocytes. *J Pathol* 2002;198: 317–25.
5. Clavel M, Vermorken JB, Cognetti F, Cappelaere P, de Mulder PH, Schornagel JH, Tueni EA, et al. Randomized comparison of cisplatin, methotrexate, bleomycin and vincristine (CABO) versus cisplatin and 5-fluorouracil (CF) versus cisplatin (C) in recurrent or metastatic squamous cell carcinoma of the head and neck: phase III study of the EORTC Head and Neck Cancer Cooperative Group. *Ann Oncol* 1994;5:521–6.
6. Morton RP, Rugman F, Dorman EB, Stoney PJ, Wilson JA, McCormick M, Veevers A, et al. Cisplatinum and bleomycin for advanced or recurrent squamous cell carcinoma of the head and neck: a randomised factorial phase III controlled trial. *Cancer Chemother Pharmacol* 1985;15:283–9.
7. Colevas AD. Chemotherapy options for patients with metastatic or recurrent squamous cell carcinoma of the head and neck. *J Clin Oncol* 2006;24:2644–52.
8. Ardalan B, Chua L, Tian EM, Reddy R, Sridhar K, Benedetto P, Richman S, et al. A phase II study of weekly 24-hour infusion with high-dose fluorouracil with leucovorin in colorectal carcinoma. *J Clin Oncol* 1991;9:625–30.
9. Chi KH, Chan WK, Shu CH, Law CK, Chen SY, Yen SH, Chen KY. Elimination of dose-limiting toxicities of cisplatin, 5-fluorouracil, and leucovorin using a weekly 24-hour infusion schedule for the treatment of patients with nasopharyngeal carcinoma. *Cancer* 1995;76:2186–92.
10. Delaunoit T, Marechal R, Hendlisz A, Eisendrath P, Legendre H, Pector JC, Becker D, et al. Treatment of advanced digestive non-colon cancer with a weekly 24-hour infusion of high-dose 5-fluorouracil modulated by folinic acid and cisplatin: an easy-to-use and well-tolerated combination. *Anticancer Drugs* 2004; 15:725–8.
11. Hsu CH, Cheng AL, Hsu C, Yang CH, Lu YS, Lin CC, Bu CF, et al. A phase II study of weekly methotrexate, cisplatin, and 24-hour infusion of high-dose 5-fluorouracil and leucovorin (MP-HDFL) in patients with metastatic and recurrent esophageal cancer-improving toxicity profile by infusional schedule and double biochemical modulation of 5-fluorouracil. *Anticancer Res* 2002;22:3621–7.
12. Hsu CH, Yeh KH, Chen LT, Liu JM, Jan CM, Lin JT, Chen YC, et al. Weekly 24-hour infusion of high-dose 5-fluorouracil and leucovorin in the treatment of advanced gastric cancers: effective and low-toxicity regimen for patients with poor general condition. *Oncology* 1997;54:275–80.
13. Stickel F, Jüngert B, Brueckl V, Schirner I, Brueckl WM, Männlein G, Hegewald J, et al. Weekly high-dose 5-fluorouracil as 24-hour infusion and folinic acid (AIO) plus irinotecan as second- and third-line treatment in patients with colorectal cancer pre-treated with AIO plus oxaliplatin. *Anticancer Drugs* 2003;14:745–9.
14. Yeh KH, Cheng AL, Lin MT, Hong RL, Hsu CH, Lin JF, Chang KJ, et al. A phase II study of weekly 24-hour infusion of high-dose 5-fluorouracil and leucovorin (HDFL) in the treatment of recurrent or metastatic colorectal cancers. *Anticancer Res* 1997;17:3867–71.
15. Bertino JR, Mini E, Fernandes DJ. Sequential methotrexate and 5-fluorouracil: mechanisms of synergy. *Semin Oncol* 1983;10:2–5.
16. Caponigro F, Comella P, Marcolin P, Spena FR, Biglietto M, Carteni G, Lucia LD, et al. A phase II trial of cisplatin, methotrexate, levofolinic acid, and 5-fluorouracil in the treatment of patients with locally advanced, metastatic squamous cell carcinoma of the head and neck. *Cancer* 1999;85:952–9.

17. Ringborg U, Ewert G, Kinnman J, Lundqvist PG, Strander H. Sequential methotrexate-5-fluorouracil treatment of squamous cell carcinoma of the head and neck. *Cancer* 1983;52:971–3.
18. Stabuc B, Markovic A, Plesnicar A, Cizej TE. Double modulation of 5-fluorouracil by leucovorin and low-dose methotrexate in advanced colorectal cancer. *Neoplasma* 2000;47:248–52.
19. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–16.
20. Forastiere AA, Metch B, Schuller DE, Ensley JF, Hutchins LF, Triozzi P, Kish JA, et al. Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous-cell carcinoma of the head and neck: a Southwest Oncology Group study. *J Clin Oncol* 1992; 10:1245–51.
21. Gibson MK, Li Y, Murphy B, Hussain MH, DeConti RC, Ensley J, Forastiere AA. Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395): an intergroup trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 2005; 23:3562–7.
22. Jacobs C, Lyman G, Velez-Garcia E, Sridhar KS, Knight W, Hochster H, Goodnough LT, et al. A phase III randomized study comparing cisplatin and fluorouracil as single agents and in combination for advanced squamous cell carcinoma of the head and neck. *J Clin Oncol* 1992;10:257–63.
23. Schrijvers D, Johnson J, Jiminez U, Gore M, Kosmidis P, Szpirglas H, Robbins K, et al. Phase III trial of modulation of cisplatin/fluorouracil chemotherapy by interferon alfa-2b in patients with recurrent or metastatic head and neck cancer. Head and Neck Interferon Cooperative Study Group. *J Clin Oncol* 1998;16:1054–9.
24. Cheng AL, Yeh KH, Lin JT, Hsu C, Liu MY. Cisplatin, etoposide, and weekly high-dose 5-fluorouracil and leucovorin infusion (PE-HDFL): a very effective regimen with good patient compliance for advanced gastric cancer. *Anticancer Res* 1998;18: 1267–72.
25. Bagrij T, Kralovanszky J, Gyergyay F, Kiss E, Peters GJ. Influence of uridine treatment in mice on the protection of gastrointestinal toxicity caused by 5-fluorouracil. *Anticancer Res* 1993;13:789–93.