Liposomal pegylated doxorubicin and oxaliplatin as salvage chemotherapy in patients with metastatic gastric cancer treated earlier

Francesco Recchia[a,b], Giampiero Candeloro[a], Gabriele Guerriero[b], Juan Piazze[b], Giovambattista Desideri[c], Stefano Necozione[d] and Silvio Rea[b,e]

The aim of this study was to evaluate the activity and safety of pegylated liposomal doxorubicin (PLD) and oxaliplatin (LOHP) as salvage chemotherapy in patients with metastatic gastric cancer (MGC) who had earlier been treated with docetaxel, capecitabine, 5-fluorouracil, and leucovorin. Treatment consisted of PLD (40 mg/m^2) and LOHP (120 mg/m^2) administered over 2 days, every 3 weeks. Response to therapy was assessed using the Response Evaluation Criteria In Solid Tumors; toxicity was evaluated by the National Cancer Institute common toxicity criteria (version 2.0). Thirty-six patients with pretreated MGC and a mean age of 66 years were recruited for the study. After a median follow-up of 11 months and 202 courses of chemotherapy administered (median, five courses per patient), the overall response rate in the 36 evaluable patients was estimated to be 28%. Grades 3 and 4 hematological toxicities were neutropenia in 44% of patients, grade 2–3 diarrhea in 14% of patients, and grade 2 neuropathy in 12 patients. Median progression-free survival and overall survival were 5.8 and 9.2 months, respectively, with 1-year survival rate of 36%, [95% confidence interval (CI): 21–54%]. Median survival time from the diagnosis of metastatic disease was 31.5 months. Seventy-two percent of patients ($n=26$) (95% CI: 58–88%) obtained a clinical benefit from this chemotherapy regimen. PLD and LOHP is an active regimen, able to give palliation in a substantial percentage of MCG patients who have been pretreated with taxanes. *Anti-Cancer Drugs* 21:559–564 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2010, **21**:559–564

Keywords: oxaliplatin, pegylated liposomal doxorubicin, pretreated metastatic gastric cancer, second-line chemotherapy

[a]Ospedale Civile di Avezzano, Unità operativa di Oncologia, [b]Fondazione Carlo Ferri, Monterotondo, Roma, [c]Geriatria, [d]Epidemiologia Clinica and [e]Chirurgia Oncologica, Università degli Studi dell'Aquila, Italy

Correspondence to Francesco Recchia, MD, Strada Del Castagneto n. 15, 67056 Luco dei Marsi (AQ), Italy
Tel: +39 863 499250; fax: +39 863 499388;
e-mail: frecchia1946@libero.it

Received 7 December 2009 **Revised form accepted** 15 February 2010

Introduction

Despite major declines in the incidence and mortality over several decades, stomach cancer remains the fourth most common cancer and the second most common cause of cancer death in the world [1]. On account of the marked geographical variation in incidence, countries with lower rates (such as North America, Western Europe, and Australia) lack public awareness of this disease and do not adopt the screening procedures that we observe in countries with high rates of stomach cancer (such as China and Japan). For this reason and because of the absence of specific symptoms, about two-thirds of the patients with gastric cancer in the Western world are diagnosed at a late stage.

When surgical resection is possible, it is curative in less than 40% of cases [2]; adjuvant chemo-radiotherapy may prolong median survival by approximately 9 months [3]. However, the disease is incurable once it has become metastatic, and the 5-year survival rate is usually less than 4% [4]. The addition of new drugs such as docetaxel to old compounds such as cisplatin and 5-fluorouracil (5-FU) has significantly improved chemotherapy results for patients with metastatic disease [5]. Encouraging results have been obtained by adding bevacizumab to chemotherapy [6].

The results of second-line chemotherapy are scant and there is no standard treatment for patients whose disease progresses after first-line chemotherapy [7]. Usually, these are patients with a poor performance status and precarious nutritional conditions who do not tolerate the toxicity of chemotherapy. For this reason, we performed this phase II study using two relatively new drugs: pegylated liposomal doxorubicin (PLD) and oxaliplatin (LOHP). These drugs belong to two classes of chemotherapeutic compounds (anthracyclines and platinum analogs, respectively) that are active in the treatment of advanced gastric cancer, but are devoid of the toxicity of their respective parent compounds, doxorubicin, and cisplatin. Anthracyclines may enhance the cytotoxicity of chemotherapy in the treatment of metastatic gastric cancer (MGC) when they are added to a combination of bolus 5-FU and cisplatin [8]. In addition, LOHP has been shown, *in vitro*, to be active on gastric cancer cell lines [9], and, *in vivo*, to be as effective as cisplatin in the treatment of patients with advanced gastric cancer, with a better toxicity profile [10].

0959-4973 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/CAD.0b013e328338b6a5

Another reason for combining anthracyclines and platinum analogues is that their different mechanisms of action decrease the likelihood of cross-resistance: LOHP creates DNA adducts, whereas anthracyclines involve DNA intercalation and topoisomerase II inhibition [11]. Moreover, liposome technology has helped to decrease drug toxicity. Encapsulation of doxorubicin by stealth pegylated liposomes (Caelyx) reduces its uptake by the reticuloendothelial system; this prolongs its serum half-life to approximately 50 h, compared with 10 min for the nonencapsulated drug [12]. As a result, PLD causes less myelotoxicity, cardiotoxicity, nausea, vomiting, and alopecia than its parent compound, doxorubicin [13], whereas LOHP lacks the renal toxicity that characterizes cisplatin. In a phase II study, PLD was combined with mitomycin C, 5-FU, and folinic acid in the treatment of advanced gastric cancer. Results obtained were promising, with an overall response rate of 47%, a median time to progression and overall survival (OS) of 8.4 and 14.7 months, respectively [14].

We have reported earlier the first-line treatment of 41 MGC patients with docetaxel administered every 4 weeks, and a De Gramont-like regimen administered every 2 weeks [15]. Patients who achieved clinical benefit from this chemotherapy were treated with low-dose interleukin-2 and 13-*cis*-retinoic acid as maintenance immunotherapy. The overall response rate was estimated to be 49%, whereas median progression-free and OS were 9.5 and 21.1 months, respectively. When these patients progressed they were treated with the current salvage chemotherapy regimen. The doses of the combination of PLD and LOHP were determined in a phase I study [16] and have been successfully used as second-line chemotherapy to treat recurrent ovarian cancer [17].

Patients and methods

Patient eligibility

Patients were eligible for the study if they had histologically confirmed recurrent or metastatic adenocarcinoma of the stomach with the following characteristics: (i) age more than 18 years, (ii) Eastern Cooperative Oncology Group performance status less than 2, (iii) disease progression after first-line chemotherapy for metastatic disease within 3 months before study enrollment, (iv) evaluable disease with or without a measurable lesion, (v) life expectancy of 3 months or greater, (vi) adequate baseline bone marrow function (absolute neutrophil count $\geq 1500/\mu l$, platelet count $\geq 100\,000/\mu l$), (vii) adequate baseline hepatic function [serum bilirubin ≤ 2.0 mg/dl, transaminase (aspartate aminotransferase, alanine transaminase) $\leq 5 \times$ the upper limit of institutional normal in the presence of liver metastases], and (viii) adequate renal function (creatinine ≤ 1.5 mg/dl). Patients were excluded if they had other malignancies other than curatively treated skin and cervical cancer, brain metastases, peripheral neuropathy as determined by the National Cancer Institute common toxicity criteria grade greater than 2, severe comorbid conditions, or lacked the ability to comply with the requirements of the protocol. This phase II study, conducted in accordance with the Declaration of Helsinki and the EU Guidelines on Good Clinical Practice, was approved by the local Ethics Committee, and written informed consent was obtained from each patient.

Treatment

First-line chemotherapy, described earlier [15], consisted of docetaxel (75 mg/m^2) on day 1, leucovorin (200 mg/m^2), 5-FU (400 mg/m^2), and capecitabine (2000 mg/m^2) on days 1, 2, 14, and 15. Patients with complete or partial response and disease stability underwent treatment with self-administered subcutaneous IL-2 at a dosage of 1.8×10^6 IU daily at bedtime, 5 days/week, and oral 13-*cis* retinoic acid at a dose of 0.5 mg/kg body weight, administered with meals for 5 days/week for 3 weeks each month. Patients exhibiting evidence of disease progression were treated with the following: a 2-day schedule outpatient salvage chemotherapy, which was repeated every 3 weeks; 15-minute intravenous (i.v.) administration of dexamethasone (20 mg) and a 5-HT3 antagonist in 100 cm^3 of saline; 1-h administration of 20 mEq KCl and 4 mEq $MgSO_4$. PLD was administered i.v. in 1 h at a dose of 20 mg/m^2 (total dosage in 2 days: 40 mg/m^2) diluted in 250 ml of 5% dextrose in water [16]. Both hands and feet were refrigerated during PLD administration to decrease the occurrence of palmar–plantar erythrodysesthesia (PPE). LOHP was administered i.v. after PLD in 2 h at the dose of 60 mg/m^2 (total dosage in 2 days: 120 mg/m^2) in 500 cm^3 of a 5% glucose solution. Acetyl-L-carnitine was administered orally (500 mg twice a day) to decrease the likelihood of neuropathy. Chemotherapy was discontinued in cases of disease progression, unacceptable toxicity, or patient refusal. Granulocyte colony-stimulating factor and erythropoietin were used if febrile neutropenia or grade 3 anemia were recorded in the earlier course of chemotherapy.

Dose modifications

Given that this study involved two agents, dose adjustments were made for each agent if a distinction in toxicity could be made. If both agents were believed to be causing toxicity, a dose reduction was performed for both groups of agents. If grade 3 or 4 myelosuppression occurred, the PLD dose was decreased by 10%; in cases of grade 3 or 4 gastrointestinal toxicity, the dose of LOHP was withheld; subsequent doses, decreased by 20%, were resumed when toxicity was resolved. Under no circumstances were the drug doses increased.

Pre-treatment evaluations

Pre-treatment evaluation included medical history, clinical examination, complete blood cell count, assessment of plasma urea and creatinine levels, electrolyte measurement,

a liver function test, serum carcinoembryonic antigen and carbohydrate antigen 19.9, electrocardiogram, and computed tomographic scan of the chest and upper abdomen. Radiographs of abnormal areas of bone scan uptake were taken within 1 month before the start of chemotherapy. Before each subsequent course of treatment, all patients had plasma urea, electrolytes, serum creatinine, alanine transaminase, aspartate aminotransferase, alkaline phosphatase, and bilirubin measurements taken. In addition, a blood cell count was repeated weekly.

Response and toxicity evaluation

Response Evaluation Criteria in Solid Tumors were used to assess patients' responses to treatment [18]. Relapse was defined as either the recurrence of a former lesion, the enlargement of a preexisting lesion, or the formation of new lesions including central nervous system disease, after a period of response. The date of relapse was defined as the time when recurrent disease was diagnosed. Progression-free survival (PFS) was defined as the length of time from the date of the first course of therapy to any relapse, or to the appearance of a second primary cancer or death, whichever occurred first. PFS and OS were estimated by means of the Kaplan–Meier product-limit method [19]. OS was measured from study entry to death or to October 31, 2009 for censored patients. If the disease had not progressed by the time of this analysis, PFS was considered censored at that date. The National Cancer Institute common toxicity (version 2.0) criteria for assessing toxicity were used.

Statistical considerations

Accrual was conducted in two stages, according to Simon's optimal two-stage design [20]. The primary endpoint of the study was the improvement of OS with respect to historical controls in the literature [7]. The first stage required that at least two of 18 patients have a confirmed OS improvement of 50%, from 5.6 to 8.4 months, to rule out an undesirably low response probability of 0.1 (P0) in favor of a desirable probability of 0.30 (P1), with a 5% probability of accepting a poor agent ($a = 0.05$) and a 10% probability of rejecting a good agent ($b = 0.10$). In the second stage, accrual to a total of 34 assessable patients would provide the desired outcome if a total of six or more patients showed a confirmed improvement in OS, then the primary endpoint would have been met. The secondary endpoints included response rate, PFS, and 1-year survival rate. Statistical analysis was performed with SAS statistical software (version 8.12, 2000, SAS Institute Inc., Cary, North Carolina, USA).

Results

Patients' characteristics

Between March 2006 and December 2008, 36 patients were enrolled into the study. Twenty-three patients were progressing after a median time of 23.5 months of immunotherapy, whereas 13 patients had not responded to first-line chemotherapy. All patients who had received at least two cycles of chemotherapy were assessable for the safety analysis, response, PFS, and OS. Patients' characteristics are summarized in Table 1. In this patient population, all tumors were localized in the gastric body. The median Eastern Cooperative Oncology Group performance status was 1. Eleven patients had two or more metastatic sites. In addition, metastatic sites included liver and peritoneum in 61 and 42% of instances, respectively. Twelve patients (33%) had stage IV disease at the time of primary diagnosis, and had undergone either a palliative surgical procedure (five patients) or an exploratory laparotomy (seven patients). Twenty-four patients (66%), who had been radically operated upon, had a median disease-free interval of 23 months (range, 0.5–126 months) from the primary surgery.

Table 1 Characteristics of patients

Characteristics	*N* (%)
No. of patients	36 (100)
Age (years)	
Median	68
Range	48–84
Performance status (ECOG)	
0–1	30 (11)
2	6 (17)
Stage at diagnosis	
II	4 (11)
III	20 (56)
IV	12 (33)
DFI	23 months (0.5–84)
Grading	
G2	15 (42)
G3	21 (58)
Earlier courses of chemotherapy	
I line	19 (53)
II lines	17 (47)
Metastatic sites	
Liver	22 (61)
Lung	4 (11)
Abdomen	15 (42)
Bone	5 (14)
Nodes	9 (25)

DFI, disease free interval; ECOG, Eastern Cooperative Oncology Group.

Treatment

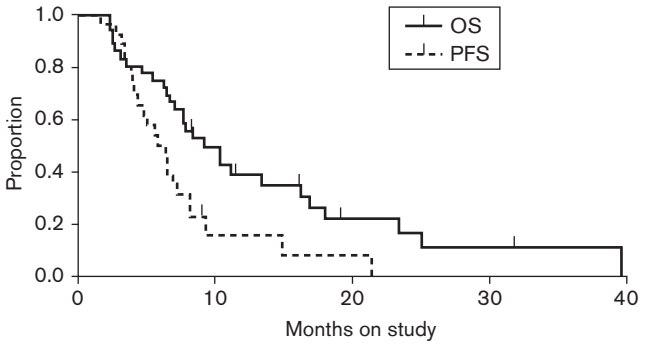
The 36 evaluable patients had had a median PFS of 9.5 months and a median OS of 21.1 months. When they were enrolled into the study a sustained improvement of evaluated immunological parameters with a negligible toxicity profile was observed in the 27 patients treated with interleukin-2 and 13-*cis*-retinoic acid. The 2-year survival rate was 42%. A total of 202 cycles of chemotherapy were administered to the 36 evaluable patients, with a median of five cycles per patient (range, 2–19). The respective planned dose intensities of LOHP and PLD were 40 and 13.3 mg/m^2/week. The median delivered dose intensities of LOHP and PLD were 94 and 95% of the respective planned doses. Sixteen patients had dose reductions because of grade 3–4 neutropenia and grade 3 gastrointestinal toxicity. Thirteen cycles were delayed because of mucositis ($n = 2$), neutropenia

($n = 9$), and diarrhea ($n = 2$). After progression with this regimen, eight patients were treated with 5-FU-carboplatin continuous infusion [21] and 15 patients were treated with irinotecan-based chemotherapy.

Antitumor activity

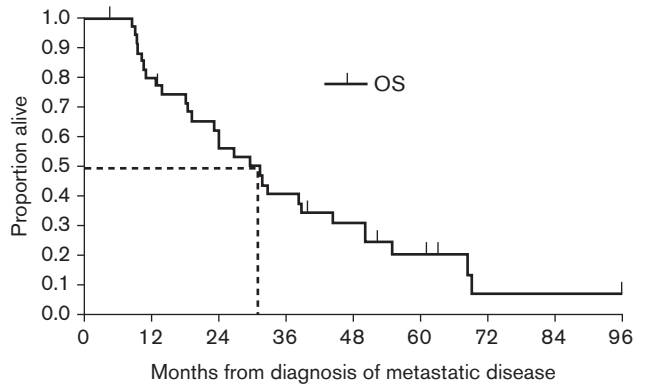
All responses were reviewed by an external radiologist. The responses were as follows: partial response, 10 patients [28%, 95% confidence interval (CI): 14–45%]; stable disease, 16 patients (44%, 95% CI: 28–61%); progressive disease, 10 patients (28%, 95% CI: 14–45%). After a median follow-up of 11 months for living patients (range, 6–39 months), 33 patients (92%) had disease progression and 28 patients (78%) had died. Median PFS was 5.8 months (range, 2–21 months) (Fig. 1). Median OS was 9.2 months (range, 2.3 to 36.9+ months) (Fig. 1).

Fig. 1



Progression-free survival (PFS) and overall survival (OS). PFS: censored patients: three (8%); progression events: 33 (92%); median PFS: 5.8 months. OS: censored patients: eight (22%); death events: 28 (78%); median OS: 9.2 months; 1-year survival rate: 38%.

Fig. 2



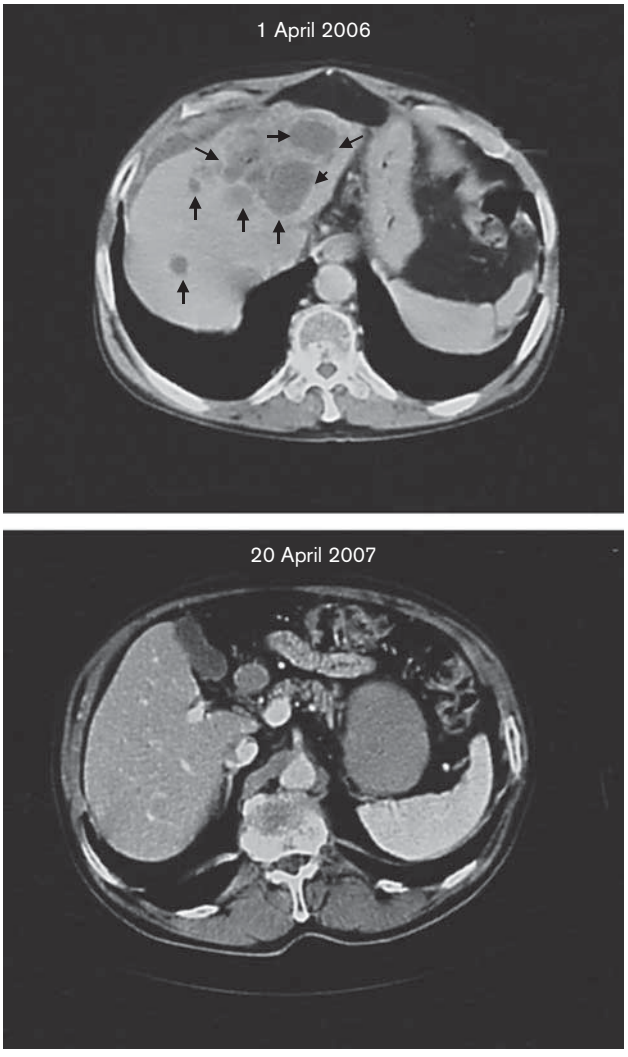
Overall survival (OS) from the diagnosis of metastatic disease. Censored patients: eight (22%); death events: 28 (76%); median OS: 31.5 months.

The 1-year survival rate of all patients was 36%, (95% CI: 21–54%). If we consider the date of the first chemotherapy for metastatic disease, median OS was 31.5 months (range, 4.7 to 96+ months) (Fig. 2). A remarkable response of liver metastases was observed in one patient who had had disease stability after four courses of first-line chemotherapy with docetaxel, leucovorin, 5-FU, and capecitabine. This patient received 16 courses of the study chemotherapy and continued to improve till a complete response was achieved (Fig. 3).

Toxicity

All 36 patients were assessed for toxicity (Table 2). No treatment-related deaths were observed. Grade 3–4 neutropenia occurred in 16 patients (44%), grade 1–2

Fig. 3



Hepatic metastases stable after first-line chemotherapy (docetaxel De Gramont), and complete response to pegylated liposomal doxorubicin and oxaliplatin.

Table 2 Toxicity according to WHO criteria

	WHO grade					
	N (%)					
	0	1	2	3	4	Total
Hematologic						
Leucopenia	2 (6)	17 (47)	9 (25)	8 (22)	0 (0)	36 (100)
Neutropenia	1 (3)	9 (25)	10 (27)	10 (27)	6 (17)	36 (100)
Thrombocytopenia	36 (100)	0 (0)	0 (0)	0 (0)	0 (0)	36 (100)
Anemia	12 (33)	17 (47)	7 (20)	0 (0)	0 (0)	36 (100)
Infection	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Gastrointestinal						
Oral	28 (78)	8 (22)	0 (0)	0 (0)	0 (0)	36 (100)
Nausea and vomiting	29 (80)	6 (17)	1 (3)	0 (0)	0 (0)	36 (100)
Diarrhea	21 (58)	12 (33)	3 (9)	0 (0)	0 (0)	36 (100)
Hepatic	34 (94)	1 (3)	1 (3)	0 (0)	0 (0)	36 (100)
PPE	23 (64)	10 (28)	2 (5)	1 (3)	0 (0)	36 (100)
Neurotoxicity	23 (64)	9 (25)	4 (11)	0 (0)	0 (0)	36 (100)
Cutaneous						
Alopecia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Skin	23 (64)	8 (22)	5 (14)	0 (0)	0 (0)	36 (100)

PPE, palmar–plantar erythrodysesthesia.

anemia in 24 patients (67%), and grade 1–2 thrombocytopenia in two patients (6%); grade 2–3 diarrhea was seen in five patients (14%), grade 3 mucositis in four patients (11%); grade 1–2 neurotoxicity in 12 patients (33%), and grade 2 PPE in three patients (8%).

Discussion

On account of the uncertain benefits of chemotherapy, and in the absence of randomized trials of chemotherapy versus best supportive care alone, there is currently no regimen that can be considered as standard for the second-line treatment of MGC. Nevertheless, it has been shown that response rates to second-line therapy in phase II trials are similar to those seen in the context of other more common cancers and that patients who respond to second-line therapy survive longer and have a more pronounced symptomatic benefit compared with nonresponders [7].

Owing to the poor performance status that patients with advanced gastric cancer usually have, palliation of their disease may require a chemotherapy regimen that is devoid of excessive toxicity. Therefore, we have chosen two drugs, PLD and LOHP that have shown some activity and are not inferior to their more toxic parent compounds. In fact, LOHP has shown an activity not inferior to cisplatin when used as first-line chemotherapy in patients with MGC [10]. However, in this study, a subgroup analysis of patients older than 65 years of age favored the LOHP combination with improved response rate, time-to-treatment failure, PFS, and OS compared with the cisplatin regimen. As second-line chemotherapy, LOHP (75 mg/m^2) on day 1 was combined with 5-FU (1000 mg/m^2) and leucovorin (20 mg/m^2) on days 1–3, every 3 weeks. After a total of 203 cycles of chemotherapy were administered, the median OS was 6.6 months, the median PFS was 2.5 months, and the disease control rate was 48% (95% CI: 34–62%). Grade 3/4 neutropenia was observed in 16 patients [22].

In another study, LOHP was added to docetaxel as second-line treatment after the failure of fluoropyrimidine. The 48 patients enrolled in the study had a partial response of 22.9%, whereas the median time to progression and OS were 4.4 and 7.2 months, respectively [23]. Significant hematologic toxicity was noted with grade 3 and grade 4 neutropenia, and grade 3 thrombocytopenia.

Several other drugs have been used as second-line chemotherapy to treat MGC, including irinotecan and docetaxel. In one study [24], 49 patients with earlier treated metastatic or recurrent advanced gastric cancer were treated with a combination chemotherapy of irinotecan and docetaxel. The median time to progression for all patients was 2.7 months (95% CI: 1.7–3.8 months) and the median OS was 8.9 months (95% CI: 6.6–11.3 months). Hematologic toxicity was severe with two possible treatment-related deaths.

Irinotecan was also combined with the monoclonal antibody, cetuximab, and given in a phase II study to 28 patients with heavily pretreated gastric cancer who had been analyzed for K-ras mutations. The overall response rate to cetuximab and chemotherapy was 3.6%, with a modest median PFS and OS of 1.7 and 3.2 months, respectively [25].

The results of this study show that the combination of PLD and LOHP has activity in second-line chemotherapeutic treatment of MGC. Our response rates were modest and no complete responses were observed, but we were able to palliate a substantial proportion of patients (26 patients, 72%) with partial response or stable disease. Median PFS was 5.8 months, and median OS was 9.2 months, indicating a role for this chemotherapy regimen in this patient population. In addition, the median survival time from the start of first-line chemotherapy was unusually long: 31 months (Fig. 2). This uncommon OS might be because of the maintenance immunotherapy that we adopted after first-line chemotherapy [15]. We treated patients with a first-line chemotherapy regimen: a combination of docetaxel and a De Gramont-like regimen. Our response rates were similar to those obtained in the V325 study [5].

Treatment was relatively well tolerated in our trial, with the predominant grade 3–4 toxic effects being neutropenia in 16 patients, but only two of them developed febrile neutropenia. The fractionated administration of LOHP was probably the reason for the low neurological toxicity observed, as we have reported [26,27]. One possible reason of the recorded low rate of severe neuropathy could be found in the fractionated administration over 2 days of the drug. Moreover, neuromodulatory agents have been administered to patients to prevent LOHP-induced

neurotoxicity. The reason for the low occurrence of PPE might be because of the fractionated dose of PLD and to the refrigeration of the extremities during drug administration.

In conclusion, salvage chemotherapy with LOHP and PLD, in patients who have MGC and have been pre-treated with taxanes, is active and gives a substantial palliation with an acceptable toxicity profile.

References

1 Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; **55**:74–108.

2 Cuschieri A, Weeden S, Fielding J, Bancewicz J, Craven J, Joypaul V, *et al.*; Surgical Co-operative Group. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. *Br J Cancer* 1999; **79**:1522–1530.

3 Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, *et al.* Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001; **345**:725–730.

4 Jemal A, Clegg LX, Ward E, Ries LA, Wu X, Jamison PM, *et al.* Annual report to the nation on the status of cancer, 1975–2001, with a special feature regarding survival. *Cancer* 2004; **101**:3–27.

5 Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, *et al.* Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol* 2006; **24**:4991–4997.

6 Shah MA, Ramanathan RK, Ilson DH, Levnor A, D'Adamo D, O'Reilly E, *et al.* Multicenter phase II study of irinotecan, cisplatin, and bevacizumab in patients with metastatic gastric or gastroesophageal junction adenocarcinoma. *J Clin Oncol* 2006; **24**:5201–5206.

7 Wilson D, Hiller L, Geh JI. Review of second line chemotherapy for advanced gastric adenocarcinoma. *Clin Oncol (R Coll Radiol)* 2005; **17**:81–90. Review.

8 Kyoto Research Group for Chemotherapy of Gastric Cancer. Randomized, comparative study of combination chemotherapy in advanced gastric cancer: 5-fluorouracil and cisplatin (FP) versus 5-fluorouracil, cisplatin and 4′-epirubicin (FPEPIR). *Anticancer Res* 1988; **12**:1983–1988.

9 Raymond E, Lawrence R, Izbicka E, Faivre S, Von Hoff DD. Activity of oxaliplatin against human tumor colony-forming units. *Clin Cancer Res* 1998; **4**:1021–1029.

10 Al-Batran SE, Hartmann JT, Probst S, Schmalenberg H, Hollerbach S, Hofheinz R, *et al.* Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. *J Clin Oncol* 2008; **26**:1435–1442.

11 Smith PJ, Soues S. Multilevel therapeutic targeting by topoisomerase inhibitors. *Br J Cancer* 1994; **23** (**Suppl**):s47–s51.

12 Gabizon A, Catane R, Uziely B, Kaufman B, Safra T, Cohen R, *et al.* Prolonged circulation time and enhanced accumulation in malignant exudates of doxorubicin encapsulated in polyethylene-glycol coated liposomes. *Cancer Res* 1994; **54**:987–992.

13 Safra T, Muggia F, Jeffers S, Tsao-Wei DD, Groshen S, Lyass O, *et al.* Pegylated liposomal doxorubicin (doxil): reduced clinical cardiotoxicity in patients reaching or exceeding cumulative doses of 500 mg/m^2. *Ann Oncol* 2000; **11**:1029–1033.

14 Gnad-Vogt SU, Hofheinz RD, Saussele S, Kreil S, Willer A, Willeke F, *et al.* Pegylated liposomal doxorubicin and mitomycin C in combination with infusional 5-fluorouracil and sodium folinic acid in the treatment of advanced gastric cancer: results of a phase II trial. *Anticancer Drugs* 2005; **16**:435–440.

15 Recchia F, Saggio G, Candeloro G, Cesta A, Amiconi G, Blasio AD, *et al.* Chemoimmunotherapy in the treatment of metastatic gastric cancer. *Anticancer Drugs* 2007; **18**:597–604.

16 Recchia F, De Filippis S, Saggio G, Amiconi G, Cesta A, Carta G, *et al.* Phase I study of liposomal doxorubicin and oxaliplatin as salvage chemotherapy in advanced ovarian cancer. *Anticancer Drugs* 2003; **14**:633–638.

17 Recchia F, Saggio G, Amiconi G, Di Blasio A, Cesta A, Candeloro G, *et al.* A multicenter phase II study of pegylated liposomal doxorubicin and oxaliplatin in recurrent ovarian cancer. *Gynecol Oncol* 2007; **106**:164–169.

18 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, *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**:205–216.

19 Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Ass* 1958; **53**:457–481.

20 Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials* 1989; **10**:1–10.

21 Recchia F, De Filippis S, Rosselli M, Saggio G, Piccinini M, Rea S. 5-fluorouracil-carboplatin continuous infusion as salvage chemotherapy in advanced cancer. *Tumori* 2001; **87**:383–387.

22 Jeong J, Jeung HC, Rha SY, Im CK, Shin SJ, Ahn JB, *et al.* Phase II study of combination chemotherapy of 5-fluorouracil, low-dose leucovorin, and oxaliplatin (FLOX regimen) in pretreated advanced gastric cancer. *Ann Oncol* 2008; **19**:1135–1140.

23 Zhong H, Zhang Y, Ma S, Ying JE, Yang Y, Yong D, *et al.* Docetaxel plus oxaliplatin (DOCOX) as a second-line treatment after failure of fluoropyrimidine and platinum in Chinese patients with advanced gastric cancer. *Anticancer Drugs* 2008; **19**:1013–1018.

24 Sym SJ, Chang HM, Kang HJ, Lee SS, Ryu MH, Lee JL, *et al.* A phase II study of irinotecan and docetaxel combination chemotherapy for patients with previously treated metastatic or recurrent advanced gastric cancer. *Cancer Chemother Pharmacol* 2008; **63**:1–8.

25 Park SR, Kook MC, Choi IJ, Kim CG, Lee JY, Cho SJ, *et al.* Predictive factors for the efficacy of cetuximab plus chemotherapy as salvage therapy in metastatic gastric cancer patients. *Cancer Chemother Pharmacol* 2009. [Epub ahead of print]

26 Mattioli R, Massacesi C, Recchia F, Marcucci F, Cappelletti C, Imperatori L, *et al.* High activity and reduced neurotoxicity of bi-fractionated oxaliplatin plus 5-fluorouracil/leucovorin for elderly patients with advanced colorectal cancer. *Ann Oncol* 2005; **16**:1147–1151.

27 Recchia F, Rea S, Nuzzo A, Lalli A, Di Lullo L, De Filippis S, *et al.* Multicenter phase II study of fractionated bimonthly oxaliplatin with leucovorin and 5-fluorouracil in patients with metastatic colorectal cancer, pre-treated with chemotherapy. *Oncol Rep* 2003; **10**:65–69.