Annals of Oncology Advance Access published February 13, 2009

original article

Annals of Oncology
doi:10.1093/annonc/mdn766

Pemetrexed in combination with oxaliplatin as a first-line therapy for advanced gastric cancer: a multi-institutional phase II study

L. Celio[1], C. N. Sternberg[2], R. Labianca[3], I. La Torre[4], V. Amoroso[5], C. Barone[6], G. Pinotti[7], S. Cascinu[8], F. Di Costanzo[9], G. L. Cetto[10] & E. Bajetta[1]*

[1]Medical Oncology Unit 2, Foundation IRCCS National Tumour Institute, Milan; [2]Department of Medical Oncology, San Camillo Forlanini Hospital, Rome; [3]Department of Medical Oncology, Reunited Hospitals, Bergamo; [4]Medical Department, Eli Lilly Italy, Sesto Fiorentino; [5]Department of Medical Oncology, Civil Hospitals, Brescia; [6]Department of Medical Oncology, Catholic University of the Sacred Heart; [7]Department of Oncology, Circle's Hospital, Varese; [8]Department of Medical Oncology, University Hospital, Ancona; [9]Department of Medical Oncology, Careggi Hospital, Florence; [10]Department of Medical Oncology, Borgo Trento Hospital, Verona

Received 4 November 2008; revised 14 November 2008; accepted 25 November 2008

Background: This clinical trial assessed the efficacy of pemetrexed combined with oxaliplatin (PEMOX) in patients with advanced gastric cancer (AGC).

Patients and methods: Forty-four patients with untreated AGC were enrolled to evaluate response rate (RR). Patients received pemetrexed (500 mg/m^2) with vitamin supplementation and oxaliplatin (120 mg/m^2) every 21 days for six cycles or until disease progression occurred.

Results: Median age was 62 years (range 26–76). The majority of patients (93%) had metastatic disease. Sixteen of the 44 patients achieved confirmed response [RR 36%; 95% confidence interval (CI) 22% to 52%]; four complete responses and 12 partial responses (complete and partial responses according to the RECIST guidelines are the confirmed-responses observed in the study population). Median time to tumor progression (TTP) was 6.2 months (95% CI 4.3–7.5) and median survival was 10.8 months (95% CI 7.7–17.2). A total of 220 cycles were administered, with a median of six cycles. Most common grade 3/4 toxic effects were neutropenia in 41% of patients (19% of cycles) and thrombocytopenia in 11% of patients (4% of cycles). Treatment delays or dose reductions for toxicity occurred in 10% and 5% of cycles, respectively.

Conclusions: PEMOX is active and well tolerated in AGC. RR, TTP, and survival were comparable to those achieved in studies using different 5-fluorouracil (5-FU)–oxaliplatin combinations, without the inconvenience of prolonged 5-FU schedules.

Key words: advanced gastric cancer, chemotherapy, oxaliplatin, pemetrexed, phase II trial

introduction

Patients suffering from advanced gastric cancer (AGC) remain a therapeutic challenge for medical oncologists. Despite increasing evidence that the appropriate management of fit patients should be with systemic chemotherapy, no combination has yet emerged as the standard of care. To date, chemotherapy relies heavily upon 5-fluorouracil (5-FU) and/or cisplatin, with 5-FU–cisplatin (CF) and epirubicin–cisplatin–5-FU (ECF) being currently regarded as reference regimens [1]. A recent phase III study comparing docetaxel–cisplatin–5-FU (DCF) to the reference arm of CF showed that DCF improved survival significantly compared with that seen in the cohort treated with CF alone [2]. However, the DCF regimen induced severe toxicity, thereby limiting its clinical application. In addition, cisplatin-based combinations are difficult to administer in this often-debilitated population and have the potential for severe toxicity. Therefore, effective treatment regimens with acceptable toxicity profiles are needed, with increasing attention toward patient convenience and quality of life [3].

Oxaliplatin is a third-generation platinum derivative with a more favorable toxicity profile than cisplatin [4]. Oxaliplatin does not cause ototoxicity or nephrotoxicity and its administration does not require aggressive i.v. hydration. Several phase II studies have demonstrated that oxaliplatin in combination with 5-FU may be an effective and well-tolerated treatment of patients with AGC [5–9]. However, major drawbacks of oxaliplatin-based doublets are the inconvenience of the 5-FU dosing schedule and the requirement for central venous access catheter and infusion device.

The new multitargeted antifolate pemetrexed has an important advantage compared with prolonged 5-FU schedules

*Correspondence to: Dr E. Bajetta, Medical Oncology Unit 2, Fondazione IRCCS Istituto Nazionale dei Tumori, Via G. Venezian 1, 20133 Milan, Italy. Tel: +39-02-23902500; Fax: +39-02-23902149; E-mail: emilio.bajetta@istitutotumori.mi.it

in that it can be administered via a single short injection [10]. Pemetrexed has proved to be more active than 5-FU against several human gastric cancer cell lines [11]. Myelosuppression was the predominant dose-limiting toxicity of this antifolate in the clinical setting, but concomitant folic acid (FA) and vitamin B_{12} supplementation was able to markedly reduce the toxicity profile [10]. Single-agent pemetrexed has demonstrated clinical activity against several tumor types, including gastric cancer [10, 12].

Additive or synergistic cytotoxicity between pemetrexed and oxaliplatin was reported in a preclinical study [13]. Therefore, in an attempt to develop a new chemotherapeutic regimen, the combination of pemetrexed with no vitamin supplementation and oxaliplatin (PEMOX) was investigated in a phase I study, which demonstrated a safe toxicity profile of the regimen when administered using full therapeutic doses of each agent every 3 weeks in patients with solid tumors [14]. With this background, a multicenter phase II trial was conducted to evaluate the efficacy and safety of the PEMOX regimen in patients with untreated AGC.

patients and methods

patient eligibility

Patients with histologically confirmed inoperable or metastatic adenocarcinoma of the stomach or gastroesophageal junction were eligible provided they were ≥18 years of age with an Eastern Cooperative Oncology Group performance status of zero to two and had a life expectancy of at least 12 weeks. Other inclusion criteria were measurable disease according to RECIST and adequate organ function, as indicated by absolute neutrophil count $\geq 1.5 \times 10^9$/l, a platelet count $\geq 100 \times 10^9$/l, hemoglobin ≥10 g/dl, serum bilirubin ≤1.5× upper limit of normal (ULN), serum alkaline phosphatase and transaminases ≤3.0× ULN (≤5.0 × ULN if liver metastases were present), and calculated creatinine clearance (CrCl) ≥45 ml/min using the standard Cockcroft and Gault formula. No prior chemotherapy was allowed, except adjuvant chemotherapy that had been completed at least 12 months before enrollment. Exclusion criteria included brain metastases, other primary malignancy (except for *in situ* cervical cancer or adequately treated nonmelanoma skin cancer or other malignancy treated with no evidence of recurrence within 5 years before study entry), uncontrolled clinically significant effusions (pleural or peritoneal), severe comorbid conditions, and inability to interrupt nonsteroidal anti-inflammatory drugs for 2 days before and after pemetrexed administration.

All patients signed written informed consent before enrollment and the protocol was approved before commencement by the local Ethical Review Board of the participating institutions.

study design and treatment plan

This was a multicenter, nonrandomized, open-label, phase II study of PEMOX regimen. Pemetrexed 500 mg/m^2 was given as a 10-min i.v. infusion followed by oxaliplatin 120 mg/m^2 as a 2-h infusion on day 1 of a 21-day cycle, as recommended by Misset et al. [14]. Treatment was administered for six cycles but a maximum of eight cycles were permitted at the discretion of the treating physician. Reasons for early discontinuation included disease progression, unacceptable toxicity, or patient's refusal. Patients were instructed to take oral FA (350–600 μg) daily beginning 1–2 weeks before the first pemetrexed dose until 3 weeks after the final dose. Vitamin B_{12} (1000 μg i.m. injection) was administered 1–2 weeks before the first pemetrexed dose and every 9 weeks thereafter until 3 weeks after the final dose. Dexamethasone (4 mg or equivalent) was administered orally twice daily beginning the day before and ending the day after each pemetrexed dose. Antiemetic prophylaxis that included a 5-HT_3 antagonist was recommended.

study assessments

Pretreatment investigations included a complete medical history and physical examination, blood cell count, chemistry panel, urinalysis, and calculated CrCl. In addition, imaging studies were completed within 4 weeks before enrollment. Response to treatment was assessed every two cycles of therapy. Objective responses were evaluated using RECIST guidelines and were to be confirmed at least 4 weeks after the first documentation of response [15]. Blood cell counts were monitored every week; blood chemistry and calculated CrCl were assessed before each cycle. Adverse events were assessed before each cycle using National Cancer Institute—Common Toxicity Criteria (version 2.0; 1999). Peripheral neuropathy was graded according to the oxaliplatin-specific scale [16].

Drug doses were delayed and/or modified because of either absolute neutrophil count of $<0.5 \times 10^9$/l and a platelet count of $\geq 50 \times 10^9$/l (25% dose reduction) or a platelet count of $<50 \times 10^9$/l (50% reduction). Similarly, treatment was delayed because of grade 3 or 4 non-hematologic toxic effects (except for grade 3 transaminase elevation, nausea, and vomiting) or calculated CrCl <45 ml/min. When non-hematologic toxic effects resolved, therapy with pemetrexed resumed at 50% of the previous level because of grade 3 or 4 mucositis and 75% of the previous level because of grade 3 or 4 diarrhea (in the event of diarrhea, oxaliplatin dose was to be reduced to 100 mg/m^2). Treatment resumed at 25% of the previous level because of any other grade 3 or 4 non-hematologic toxicity, as appropriate. In cases of grade ≥2 neuropathy, oxaliplatin dosing was delayed until recovery and then resumed at 25% of the previous level because of first-time and second-time events lasting >7 days or discontinued if grade 3 neuropathy became persistent. Dose re-escalation was not allowed. Any patient requiring a third dose reduction or >42 days between treatments discontinued the study.

statistical considerations

The primary end point of this study was the overall response rate (ORR) to PEMOX regimen. A Simon's optimal two-stage design was used to calculate sample size with $p_0 = 0.20$ (null hypothesis) and $p_1 = 0.40$ (alternative hypothesis) with a significance level of 0.05 and a power of 80%. This resulted in a sample size of 13 patients for the first stage. If more than three objective responses were observed, further 30 patients were to be recruited in the second stage. The regimen was considered active if a total of ≥13 patients achieved a confirmed objective response. All patients who had received at least one cycle of protocol treatment were included in the response, safety, and survival analyses on an intention-to-treat basis. Time to tumor progression (TTP) was measured from the date of study enrollment to the first observation of progressive disease (PD), duration of response from the first observation of response to the first observation of PD, and overall survival (OS) from the date of study enrollment to the time of death from any cause. Time-related efficacy parameters for all patients were updated to 26 November 2007. TTP and OS were estimated using the Kaplan–Meier method. All estimates of treatment effects were conducted at a two-sided α level of 0.05 and the 95% confidence intervals (CIs) were estimated for each variable.

results

patients

From May 2004 to October 2005, 44 patients were treated at nine Italian oncology centers. Fourteen patients were enrolled at the coordinating site of Milan and the remaining 30 patients

were enrolled at the other sites. A median of four patients (range 1–14) were enrolled per site. Five patients who received study treatment did not meet eligibility criteria because of increased serum total bilirubin or alkaline phosphatase (one patient each) and decreased hemoglobin level (three patients). Baseline patient characteristics are summarized in Table 1. The median age was 62 years (range 26–76). No patients had primary tumor of gastroesophageal junction and the majority of them (29 of 44, 66%) retained the gastric lesion. The median number of organs that were involved was two (range 1–4), with 15 (34%) patients having involvement of at least three organs. Eleven of the 25 (44%) patients who underwent prior surgery received curative resection.

Table 1. Baseline patient characteristics ($n = 44$)

Characteristic	No. of patients (%)
Age, years	
≤65	24 (55)
>65	20 (45)
Sex	
Male	35 (80)
Female	9 (20)
ECOG performance status	
0	34 (77)
1	10 (23)
Treatments for primary tumor	
None	19 (43)
Surgery	20 (46)
Surgery and adjuvant chemotherapy	5 (11)
Tumor stage	
Locally advanced	3 (7)
Metastatic	41 (93)
Number of organs involved	
1	14 (32)
≥2	30 (68)
Organs involved	
Lymph nodes	31 (71)
Liver	25 (57)
Stomach	16 (36)
Lung	7 (16)
Peritoneum	6 (14)
Other[a]	11 (25)

[a]Bone (two patients), abdominal wall (one patient), adrenal gland (one patient), esophagus (one patient), mesentery (one patient), ovary (one patient), pancreas (one patient), perineum (one patient), pleura (one patient), and retroperitoneum (one patient).
ECOG, Eastern Cooperative Oncology Group.

efficacy

Discontinuation due to early disease progression occurred in one patient after the first cycle, and one further patient, who dropped out of study because of toxicity, was not assessable due to failure to obtain a follow-up tumor assessment. The details of treatment efficacy are shown in Table 2. Confirmed responses were observed in 16 out of 44 patients (ORR 36%; 95% CI 22% to 52%), with a complete response occurring in three patients with nodal metastases and one patient with liver involvement. Disease stabilization as best response was observed in 15 (34%) patients. Sites of response included liver, nodes, lung, pancreas, and ovary. Response rates (RRs) according to extension and main sites of disease are listed in Table 3.

With a median follow-up of 9.4 months (range 1.8–29.1), the median TTP was 6.2 months (95% CI 4.3–7.5). The median survival was 10.8 months (95% CI 7.7–17.2); 11 of the 44 (25%) patients were still alive at the last follow-up. Estimated 1-year survival rate was 43%.

After completion of the trial, 28 (64%) patients with disease progression received second-line chemotherapy that most frequently was as follows: a combination containing 5-FU plus irinotecan or cisplatin and docetaxel alone. One responsive patient with locally advanced disease who underwent surgery and postoperative ECF-based chemotherapy was alive at 22 months after starting protocol treatment. One further responsive patient underwent resection of a progressive ovary lesion before receiving second-line therapy.

compliance with treatment

A total of 220 treatment cycles were administered, with a median of six cycles per patient (range 1–8). Nineteen (43%) patients received six cycles of treatment; six (14%) patients received eight cycles. The median relative dose intensities were 94% for pemetrexed and 93% for oxaliplatin. The median cumulative dose was 4400 and 1050 mg for pemetrexed and oxaliplatin, respectively. There were 64 cycle delays (29% of cycles administered), but only 21 cycles were delayed due to hematologic or non-hematologic adverse events (3% and 7% of cycles, respectively). Forty-three cycles (20% of cycles) were delayed due to reasons unrelated to treatment, including scheduling conflict, patient's request, or pending imaging studies for response evaluation. Forty-three patients received more than one cycle, with 10 (23%) of them having a dose reduction in a total of 10 cycles (5% of cycles). Seven patients needed a dose reduction of both pemetrexed and oxaliplatin because of severe thrombocytopenia (four patients), vomiting (one patient), diarrhea (one patient), and fatigue (one patient). Not only the pemetrexed but also the oxaliplatin dose was reduced in one patient who developed deep vein thrombosis during the study. Pemetrexed dose was reduced in one patient due to grade 3 alanine aminotransferase elevation, whereas oxaliplatin dose was reduced in one patient due to grade 3 neurotoxicity following three cycles. The investigator decided to reduce the dose of oxaliplatin to 85% of the full dose in another patient during the first cycle.

safety

The majority of treatment-related adverse events were mild to moderate in intensity (Table 4). Grade 3/4 neutropenia occurred in 41% of patients and 19% of cycles, but no patients developed febrile neutropenia. Two patients discontinued the study because of treatment-related adverse events, one because of mucositis with dehydration after two cycles and the other because of hematologic toxicity after five cycles of therapy. A 70-year-old patient died during the study due to acute renal

Table 2. Efficacy and survival in 44 patients (intention-to-treat analysis)

Type of response (RECIST criteria)		No. of patients (%)
Complete response		4 (9)
Partial response		12 (27)
Stable disease		15 (34)
Progressive disease		12 (27)
Unknown		1 (2)
Overall response rate	36%	
95% CI	22% to 52%	
Median duration of response, months	5.7	
95% CI	5.0–6.5	
Percent of patients censored	25	
6-month response rate[a]	37.5%	
Median TTP, months	6.2	
95% CI	4.3–7.5	
Percent of patients censored	16	
6-month TTP rate[a]	54.5%	
8-month TTP rate[a]	30%	
Median survival, months	10.8	
95% CI	7.7–17.2	
Percent of patients censored	25	
12-month survival rate[a]	43%	
24-month survival rate[a]	25%	

[a]Kaplan–Meier estimates.

CI, confidence interval; TTP, time to tumor progression.

Table 3. Response according to extension and site of disease

Type of extension or site	Tumor response		
	CR + PR, *n* (%)	SD, *n* (%)	PD, *n* (%)
Assessable patients, *n* = 43	16 (37)	15 (35)	12 (28)
One organ, *n* = 14	8 (57)	2 (14)	4 (29)
Two or more organs, *n* = 29	8 (28)	13 (44)	8 (28)
Lymph nodes only, *n* = 6	3 (50)	1 (17)	2 (33)
Liver only, *n* = 5	3 (60)	–	2 (40)
Lung, *n* = 7	2 (29)	4 (57)	1 (14)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

failure that was not considered by the investigator as related to study medications.

discussion

In a multicenter setting, we explored the efficacy and safety of the PEMOX regimen as a first-line therapy for AGC. Four complete responses and 12 partial responses occurred in 44 assessable patients, with an ORR of 36%. The median TTP was 6.2 months, and median survival was 10.8 months. These results compare well with those from previously published studies using different dose schedules of 5-FU/oxaliplatin, which reported RRs from 38% to 56%, and median TTP and survival ranging from 5 to 7 months and 8 to 11 months, respectively, in patients with untreated AGC [5–9]. As in these studies, the majority of patients in the current study presented with a good performance status and metastatic disease; their median age (62 years) was in the same range as in the previously published trials. In accordance with two mentioned studies where the frequency of second-line chemotherapy was reported, the majority of our patients received second-line therapy that frequently included irinotecan or docetaxel [8, 9]. Evidence from phase II studies suggests that irinotecan-based regimens or docetaxel may have been effective in AGC patients progressing after first-line chemotherapy [17–19]. Therefore, the use of second-line therapy may have had a positive impact on survival in the study cohort. It also should be noted that response assessments were planned every two cycles of treatment, but 20% of cycles were delayed due to reasons unrelated to treatment. We cannot exclude that delayed assessments might have had an impact on the TTP in the current study.

More recently, the results of a randomized phase III trial comparing 5-FU, leucovorin plus either oxaliplatin (FLO) or cisplatin in patients with advanced disease were published [20]. Although there was only a trend toward improved progression-free survival (primary end point) with FLO, the efficacy results lend support to the view that oxaliplatin is at least as effective as cisplatin in AGC. While the usual limitations of cross-study comparisons should be taken into account, the ORR of 36% seen in the PEMOX study in a similar population of patients compares well with that observed in the FLO arm (ORR of 35%) of the German study. The median survival in patients who underwent FLO was 10.7 months (95% CI 8.5–13.9), which is comparable to the 10.8-month median survival observed in the current study (95% CI 7.7–17.2).

The toxicity profile of PEMOX was extremely favorable and resulted in a low incidence (<10%) of severe non-hematologic adverse events. In the current study, in which oxaliplatin was administered at 120 mg/m^2 every 3 weeks, grade 3 peripheral neuropathy was seen in only one patient. However, the cumulative dose of oxaliplatin delivered was low, with a median of six cycles per patient. Compliance with the treatment regimen was very good because relative dose intensity for pemetrexed and oxaliplatin was 94% and 93%, respectively. As expected with pemetrexed-containing regimens, hematologic toxicity was more frequently noted. Grade 3/4 neutropenia occurred in 41% of patients but no patients experienced neutropenic fever or infection. Grade 3/4 thrombocytopenia occurred in 11% of patients and grade 3 anemia occurred in 11% of cases. These figures are consistent with the reported findings of a phase II trial assessing PEMOX in the first-line therapy of colorectal cancer [21]. As in the previously published study, the high toxicity observed in the current study may be related to the weekly examination of blood counts carried out during the treatment period per protocol. Indeed, clinically significant hematologic toxic effects were infrequent and required dose reduction and treatment discontinuation in only 9% and 2% of the patients, respectively.

Since accrual of the current study, a meta-analysis has indicated an advantage to three-drug regimens containing 5-FU, an anthracycline, and cisplatin in the management of AGC [22]. Although the ECF regimen results to be better

Table 4. Worst toxicity by patient and cycle

Type[a]	Toxicity per patient ($n = 44$)			Toxicity per cycle ($n = 220$)	
	Grade 1–2	Grade 3	Grade 4	Grade 3	Grade 4
Hematologic, *n* (%)					
Neutropenia	21 (48)	13 (30)	5 (11)	34 (15)	8 (4)
Thrombocytopenia	22 (50)	4 (9)	1 (2)	9 (4)	1 (0.5)
Anemia	35 (80)	5 (11)	0	6 (3)	0
Non-hematologic, *n* (%)					
Nausea	16 (36)	0	0	0	0
Vomiting	13 (30)	1 (2)	0	1 (0.5)	0
Diarrhea	13 (30)	0	1 (2)	0	1 (0.5)
Mucositis	6 (14)	0	1 (2)	0	1 (0.5)
Anorexia	7 (16)	0	0	0	0
Weight loss	4 (9)	0	0	0	0
Peripheral neuropathy	12 (27)	1 (2)	–	1 (0.5)	–
↑Aspartate aminotransferase	18 (41)	0	0	0	0
↑Alanine aminotransferase	17 (39)	4 (9)	0	4 (2)	0
↑Alkaline phosphatase	23 (52)	1 (2)	0	1 (0.5)	0
Fatigue	10 (23)	3 (7)	0	7 (3)	0
Infection without neutropenia	0	2 (4.5)	0	2 (1)	0
Pruritus	0	1 (2)	0	1 (0.5)	0

[a]Graded according to National Cancer Institute—Common Toxicity Criteria, version 2.0.

tolerated among three-drug combinations, the addition of epirubicin to CF was never explored in a randomized trial. In addition, intensive regimens may represent a meaningful treatment option only for younger and fit patients [23]. A recent phase III study comparing DCF with CF demonstrated a significant superiority of DCF in terms of ORR (37% versus 25%), TTP (5.6 versus 3.7 months), and survival (9.2 versus 8.6 months) [2]. However, DCF was associated with a high incidence of severe toxicity, including neutropenia and diarrhea. More recently, in a Korean phase II study of a vitamin-supplemented combination of pemetrexed plus cisplatin, only modest activity (ORR of 26%) was seen in 50 assessable patients with untreated AGC [24]. It is worth to note that the efficacy of pemetrexed–cisplatin doublet is consistent with that (ORR of 25%) seen for protracted infusion of 5-FU plus cisplatin as reference treatment in three recently reported phase III trials in gastric cancer [2, 20, 25]. Therefore, our results and those from the Korean study indicate that oxaliplatin might represent the more appropriate platinum agent to be used in combination with pemetrexed in this malignancy.

The PEMOX regimen is active in patients with untreated AGC and is particularly attractive because of its tolerability and ease of administration. Additional trials evaluating pemetrexed given according to a once every 2-week schedule, which is the most commonly used schedule for oxaliplatin administration, may be a sound strategy for optimizing efficacy of the regimen in AGC [26]. However, PEMOX may be particularly well suited for the addition of molecular-targeted agents in the context of phase II randomized trials.

funding

Eli Lilly and Company (Study H3E-IT-S043).

acknowledgements

This study was presented in part at the 31st European Society for Medical Oncology Congress, Istanbul, Turkey, 29 September to 3 October 2006. We would like to thank Dr Angela Denaro (Medical Oncology Unit 2, National Cancer Institute, Milan) and Dr Stefania Mosconi (Department of Medical Oncology, Ospedali Riuniti, Bergamo) who participated in the study as investigators. We also thank Anne-Laure Michel (Statistical Department, Eli Lilly France) for statistical advice.

references

1. Van Cutsem E, Van de Velde C, Roth A et al. Expert opinion on management of gastric and gastro-oesophageal junction adenocarcinoma on behalf of the European Organisation for Research and treatment of Cancer (EORTC)—gastrointestinal cancer group. Eur J Cancer 2008; 44: 182–194.
2. Van Cutsem E, Moiseyenko VM, Tjulandin S 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.
3. Ajani JA. Evolving chemotherapy for advanced gastric cancer. Oncologist 2005; 10 (Suppl 3): 49–58.
4. Mani S, Graham MA, Bregman DB et al. Oxaliplatin: a review of evolving concepts. Cancer Invest 2002; 20: 246–263.
5. Louvet C, Andre T, Tigaud JM et al. Phase II study of oxaliplatin, fluorouracil, and folinic acid in locally advanced or metastatic gastric cancer patients. J Clin Oncol 2002; 20: 4543–4548.
6. Al-Batran SE, Atmaca A, Hegewisch-Becker S et al. Phase II study of biweekly infusional fluorouracil, folinic acid, and oxaliplatin in patients with advanced gastric cancer. J Clin Oncol 2004; 22: 658–663.
7. Chao Y, Yeh KH, Chang CJ et al. Phase II study of weekly oxaliplatin and 24-h infusion of high-dose 5-fluorouracil and folinic acid in the treatment of advanced gastric cancer. Br J Cancer 2004; 91: 453–458.
8. De Vita F, Orditura M, Matano E et al. A phase II study of biweekly oxaliplatin plus infusional 5-fluorouracil and folinic acid (FOLFOX-4) as first-line

treatment of advanced gastric cancer patients. Br J Cancer 2005; 92: 1644–1649.
9. Lordick F, Lorenzen S, Stollfuss J et al. Phase II study of weekly oxaliplatin plus infusional fluorouracil and folinic acid (FUFOX regimen) as first-line treatment in metastatic gastric cancer. Br J Cancer 2005; 93: 190–194.
10. Rollins KD, Lindley C. Pemetrexed: a multitargeted antifolate. Clin Ther 2005; 27: 1343–1382.
11. Kim JH, Lee KW, Jung Y et al. Cytotoxic effects of pemetrexed in gastric cancer cells. Cancer Sci 2005; 96: 365–371.
12. Bajetta E, Celio L, Buzzoni R et al. Phase II study of pemetrexed disodium (alimta®) administered with oral folic acid in patients with advanced gastric cancer. Ann Oncol 2003; 14: 1543–1548.
13. Raymond E, Louvet C, Tournigand C et al. Pemetrexed disodium combined with oxaliplatin, SN38, or 5-fluorouracil, based on the quantitation of drug interactions in human HT29 colon cancer cells. Int J Oncol 2002; 21: 361–367.
14. Misset JL, Gamelin E, Campone M et al. Phase I and pharmacokinetic study of the multitargeted antifolate pemetrexed in combination with oxaliplatin in patients with advanced solid tumors. Ann Oncol 2004; 15: 1123–1129.
15. Therasse P, Arbuck SG, Eisenhauer EA et al. New guidelines to evaluate the response to treatment in solid tumors (RECIST guidelines). J Natl Cancer Inst 2000; 92: 205–216.
16. Caussanel JP, Levi F, Brienza S et al. Phase I trial of 5-day continuous venous infusion of oxaliplatin at circadian rhythm-modulated rate compared with constant rate. J Natl Cancer Inst 1990; 82: 1046–1050.
17. Park SH, Choi EY, Bang SM et al. Salvage chemotherapy with irinotecan and cisplatin in patients with metastatic gastric cancer failing both 5-fluorouracil and taxanes. Anticancer Drugs 2005; 16: 621–625.
18. Kim ST, Kang WK, Kang JH et al. Salvage chemotherapy with irinotecan, 5-fluorouracil and leucovorin for taxane- and cisplatin-refractory, metastatic gastric cancer. Br J Cancer 2005; 92: 1850–1854.
19. Lee JL, Ryu MH, Chang HM et al. A phase II study of docetaxel as salvage chemotherapy in advanced gastric cancer after failure of fluoropyrimidine and platinum combination chemotherapy. Cancer Chemother Pharmacol 2008; 61: 631–637.
20. Al-Batran SE, Hartmann JT, Probst S 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.
21. Atkins JN, Jacobs SA, Wieand HS et al. Pemetrexed/oxaliplatin for first-line treatment of patients with advanced colorectal cancer: a phase II trial of the National Surgical Adjuvant Breast and Bowel Project Foundation Research Program. Clin Colorectal Cancer 2005; 5: 181–187.
22. Wagner AD, Grothe W, Haerting J et al. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. J Clin Oncol 2006; 18: 2903–2909.
23. Ilson DH. Docetaxel, cisplatin, and fluorouracil in gastric cancer: does the punishment fit the crime? J Clin Oncol 2007; 25: 3188–3190.
24. Kim YH, Chung HC, Kang WK et al. Pemetrexed and cisplatin in patients with advanced gastric cancer: a Korean cancer study group multicenter phase II study. Cancer Chemother Pharmacol 2008; 62: 263–270.
25. Dank M, Zaluski J, Barone C et al. Randomized phase III study comparing irinotecan combined with 5-fluorouracil and folinic acid to cisplatin combined with 5-fluorouracil in chemotherapy-naïve patients with advanced adenocarcinoma of the stomach or esophagogastric junction. Ann Oncol 2008; 19: 1450–1457.
26. Stover DG, Lockhart AC, Berlin JD et al. Phase I trial of pemetrexed plus oxaliplatin administered every other week in patients with metastatic cancer. Invest New Drugs 2008; 26: 339–345.