Treatment of Patients with Advanced Gastric Carcinoma with the Combination of Etoposide plus Oral Tegafur Modulated by Uracil and Leucovorin

A Phase II Study of the ONCOPAZ Cooperative Group

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BACKGROUND. Both the biochemical modulation and the continuous administration of 5-fluorouracil (5-FU) have achieved promising results in patients with gastric carcinoma. Conversely, several studies on gastric carcinoma have demonstrated that the combination of etoposide (VP-16), leucovorin (LV), and 5-FU (ELF) is efficacious and moderately toxic. UFT is a combination of uracil and tegafur (ftorafur) in a 4:1 molar ratio. It can be administered orally for several weeks, thus stimulating the effects of a continuous infusion of 5-FU. Its combination with LV increased the efficacy of UFT. We conducted a Phase II study on patients with gastric carcinoma using the combination VP-16-LV-UFT. This combination is administered mainly orally (p.o) and could yield a good response rate and low toxicity.

METHODS. Forty-six patients with bidimensionally measurable disease were entered into the study. Patients received VP-16 100 mg/m^2 IV on Day 1 and 200 mg/m^2 p.o. on Days 2 and 3; LV 500 mg/m^2 administered intravenously (i.v.) on Day 1, followed by p.o. LV 15 mg every twelve hours on Days 2 to 14. Patients also received UFT p.o. 390 mg/m^2/day on Days 1 to 14. Treatment was repeated every 28 days for a minimum of 3 courses per patient. All courses were given on an outpatient basis.

RESULTS. Four patients (9%) had a complete response, and 12 a partial response (26%) for an overall response rate of 35% (95% confidence interval: 22–51%). The median duration of response was 10 months. The median overall survival was 9 months. The main side effects were gastrointestinal. Grade 3 to 4 toxicity was encountered as follows: diarrhea in 17% of the patients, nausea/vomiting in 11%, anemia in 13%, mucositis and leukopenia in 4% each, and thrombocytopenia in 2%. One patient died of sepsis and neutropenia.

CONCLUSIONS. VP-16-LV-UFT has an activity comparable to that of other schemes and a low incidence of side effects. Furthermore, since it is administered mainly orally, hospitalization is avoided, which makes this scheme suitable for patients with advanced gastric carcinoma. ***Cancer* 1996; 78:211–6.**

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Gastric carcinoma is the most chemosensitive adenocarcinoma among digestive neoplasms. The following agents show a response rate of at least 15% when used alone: 5-fluorouracil (5-FU), mitomycin, semustine, carmustine, cisplatin, and adriamycin and its analogue epirubicin.[1] Combination chemotherapy including these drugs has achieved response rates of 30 to 60%.[2–5] In spite of these promising results, the responses are usually of short duration and at the cost

of high toxicity. Besides, the administration of chemotherapy requires hospitalization or the use of infusion pumps. Although some authors have suggested that chemotherapy may improve survival for patients with advanced gastric carcinoma,[6,7] its main objective is still palliative. For this reason we should give priority to the search for active and few toxic schemes that do not affect the patient's quality of life.

5-FU has been considered the mainstay of the treatment for most digestive tumors. The modulation of 5-FU with leucovorin (LV) may increase the response rate to 23 to 48%, depending on the schedule and the patient's characteristics.[8-10] The antitumor activity of 5-FU is time dependent: its half life is 15 minutes if administered by bolus, so it has been suggested that continuous infusion for several days could improve its efficacy.[11,12]

UFT contains 1-(2-tetrahydrofuryl), 5-FU (Tegafur), and uracil in a molar ratio of 4:1. Tegafur, a prodrug that is absorbed in the small intestine, is metabolized in vivo to 5-FU. Uracil inhibits the catabolism of 5-FU by the competitive inhibition of uracil dehydrogenase. This inhibition predominates in tumor cells over normal tissues, so that the combination increases the tumor concentration and antineoplastic activity.[13,14] In addition, several studies have shown that the tumor levels of 5-FU achieved after concomitant administration of uracil with tegafur are higher than levels in peripheral blood and that these are sustained for longer periods in tumor cells.[14,15] In rats, modulation of tegafur with uracil, LV or N-phosphonacetyl-L-aspartate (PALA) produces better therapeutic results than 5-FU.[16] Some studies have suggested that the oral administration of UFT is comparable to the continuous infusion of 5-FU.[17] The activity of oral tegafur alone has been demonstrated in 5-FU sensitive neoplasms.[18,19] Conversely, adjuvant therapy with tegafur decreased the relapse rate of gastric carcinoma in Japan.[20] These characteristics, along with the possibility of oral administration, make UFT an interesting alternative for the treatment of gastric carcinoma.

Some years ago we designed a scheme of chemotherapy to modulate UFT with LV.[21] Briefly, it consisted of a high dose of intravenous (i.v.) LV followed by 14 days of oral UFT and oral LV. LV is taken twice daily to maintain the folate deposits and the modulation of 5-FU metabolites. We were looking for a schedule easy to deliver on an outpatient basis, combining the advantages of modulation and prolonged administration of 5-FU. The oral administration of LV may offer an additional advantage, i.e., the selective absorption of l-isomer by the gastrointestinal tract. Thus the potentially undesirable effects of d-isomer accumulated following i.v. treatment may be avoided. It is possible that the d-isomer competes with the l-isomer, resulting in reduced efficacy. Some studies show that the levels of LV obtained either by continuous i.v. infusion or oral administration are comparable, but with a lower level of d-isomer following the latter.[22] We obtained a 39% response rate in a Phase II study performed in patients with advanced colorectal cancer.[23,24]

In gastric carcinoma, single agent therapy with etoposide achieves a 6% response rate,[1] but it acts synergistically with 5-FU. There is no cross-resistance between them.[25]

In an attempt to develop an active scheme with low toxicities for patients older than 65 years or with contraindication to anthracyclines, Wilke et al.[2] studied the combination of VP16, 5-FU, and LV. The response rate was 53%, with a good tolerance. These results and the former considerations led us to perform a multicentre cooperative trial with the combination VP-16-UFT-LV for patients with advanced gastric carcinoma.

PATIENTS AND METHODS

During the period between March 1993 and December 1994, 46 patients with histologically proven gastric carcinoma were entered into this study. Criteria for patient eligibility included histologic confirmation of adenocarcinoma of the stomach and advanced disease not potentially curable by other therapeutic modalities. All patients had a performance status of 2 or better according to Zubrod's scale (Eastern Cooperative Oncology Group [ECOG]).[26] They should have a minimum of 3 weeks recovery from any major surgical procedure involving resection or bypass or 2 weeks from exploration and biopsy only. No prior chemotherapy or prior radiation therapy was allowed. Patients were required to have a granulocyte count of $\geq 2 \times 10^9$/L and a platelet count of $> 100 \times 10^9$/L; normal renal function as defined by a serum creatinine level of < 115 μmol/L and a creatinine clearance of > 60 mL/min; and a normal hepatic function, that is, serum bilirubin of < 35 μmol/L, serum glutamic oxalacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) levels of $< 3 \times$ the upper normal limit, unless these alterations were due to metastatic disease. Patients with brain metastases or simultaneous neoplasms were excluded, except in the cases of basal cell carcinoma or in situ cervical carcinoma adequately treated. Informed consent was given by all patients according to the directives of local ethical committees.

All patients had measurable disease that was defined as the presence of at least one lesion, clearly bidimensionally measured by computed tomographic

TABLE 1
Treatment Scheme

Day 1	Leucovorin 500 mg/m^2 i.v.
	Etoposide 100 mg/m^2 i.v.
	UFT 195 mg/m^2/12h p.o.
Day 2-3	Leucovorin 15 mg/12h p.o.
	Etoposide 100 mg/m^2/12h p.o.
	UFT 195 mg/m^2/12h p.o.
Day 4-14	Leucovorin 15 mg/12h p.o.
	UFT 195 mg/m^2/12h p.o.
Cycles	Every 28 days

UFT: uracil-tegafur; i.v.: intravenous; h: hour; p.o.: orally.

TABLE 2
Patients' Characteristics

No. of patients	46
Median age in years (range)	58 (21-72)
Pretreatment ECOG PS	
0	3 (7%)
1	19 (41%)
2	24 (52%)
Locoregional/metastatic disease	4/42
Sites of metastatic disease	
Distant lymph nodes	12
Liver	24
Lung	9
Peritoneum	12
Others	21
Number of metastatic locations	
0	4 (9%)
1	15 (33%)
2	18 (39%)
3	9 (19%)

ECOG: Eastern Cooperative Oncology Group; PS: performance status.

(CT) scan, X-ray, or ultrasound. In patients with locally advanced disease, the primary tumor was evaluated by CT and endoscopy.

The study regimen consisted of: (1) VP-16 100 mg/m^2 in 50 minute i.v. infusion plus LV 500 mg/m^2 in 2 hours i.v. infusion on Day 1; (2) oral UFT 390 mg/m^2/day in 2 doses for 14 days; (3) oral VP-16 was administered on Days 2 and 3 at a dose of 200 mg/m^2/day (in 4 daily doses); (4) on Day 2, patients took oral LV, 15 mg/12 hours for 13 days. Courses were repeated every 28 days for a minimum of 3 per patient, unless progressive disease was detected (Table 1). All courses were administered on an outpatient regimen. The patients were instructed to withdraw therapy and seek medical advice if they passed 3 or more liquid stools in a day. In these cases, the dose of UFT and VP-16 was reduced by 25% in subsequent courses. If the neutrophil count was $< 1.5 \times 10^9$/L or the platelets $< 100 \times 10^9$/L, treatment was delayed for a maximum of 2 weeks. After that time, if the neutrophils were 1 to 1.5×10^9/L or the platelets were 70 to 100×10^9/L, the dose of UFT and VP-16 was reduced by 50% and if lower values resulted, chemotherapy was discontinued. In instances of Grade 3 to 4 nonhematologic toxicities, the dose of UFT and VP-16 was reduced by 25% in subsequent courses.

Response was evaluated at the end of every three courses by using World Health Organization (WHO) guidelines.[27] Re-evaluation was undertaken sooner if there was clinical evidence of progression. Complete response (CR) required the total disappearance of all tumors initially observed (determined by two observations not less than four weeks apart), with no evidence of new areas of malignant disease. Partial response (PR) was defined as a reduction of at least 50% in the sum of the products of the longest perpendicular diameter of all clearly measurable tumor masses (two observations not less than four weeks apart), with no increase in the size of any lesion and no new areas of malignant disease. Stable disease (SD) was defined as a decrease in total tumor size of $< 50\%$ or a $< 25\%$ increase in the size of 1 or more measurable lesions. Progression was defined as a 25% increase in any measurable lesion, the appearance of new areas of malignant disease, or symptomatic deterioration of the performance status by more than one level. Death due to disease progression or toxicity occurring before those dates was considered a therapeutic failure. Response duration and survival were calculated from the first day of therapy until the day of death or last known follow-up. Patients having a response were maintained on chemotherapy until progression or unacceptable toxicity occurred.

Toxicity for each course was recorded before the next treatment course and graded according to WHO scales.[27] Occasionally, the patients suffered gastric pain related to the ingestion of UFT, but the WHO scale does not include this adverse effect. So we considered it to be Grade 3 to 4 if the symptoms were intense enough to require the withdrawal of UFT in spite of the administration of antiacids or H2-blockers.

The Wilcoxon rank-sum method was used to compare quantitative variables and the chi-square for percentages. Survival and the duration of response were calculated with the Kaplan-Meier method.

RESULTS

Forty-six patients entered the study. Table 2 summarizes their characteristics. Median age was 58 years (range: 21-72). Forty-eight percent of the patients had an ECOG performance status of 0 or 1. Thirty-six (72%) presented with unresectable disease: 4 (9%) had exten-

TABLE 3
Therapeutic Results

Complete response	4 (9%)
Partial response	12 (26%)
Stable disease	8 (17%)
Progression	21 (46%)
Nonevaluable	1 (2%)

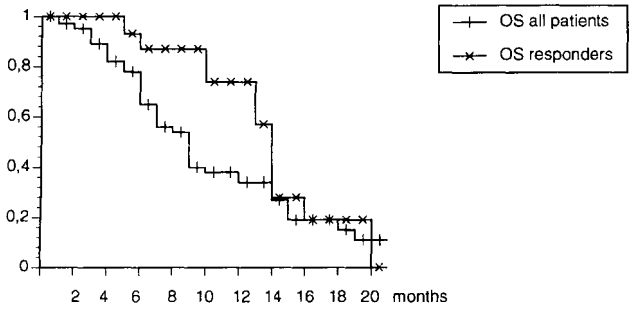

FIGURE 1. Overall survival for the whole group and for those patients who responded to chemotherapy is shown. The median survival was 9 months for all patients, and 13 months for responders.

sive local infiltration, assessed by laparotomy, and 29 (63%) had metastatic disease. The other 13 (28%) presented with relapses after radical surgery.

A total of 232 cycles of VP-16-UFT-LV were given to 46 patients (median: 5 courses/patient; range: 1–14). Two patients received just one course of chemotherapy: one died owing to toxicity and the other decided to discontinue therapy after the first course. This last patient was valid to assess toxicity but not the response.

In all, 4 patients (9%) achieved a CR and 12 (26%) a PR, for an overall response rate of 35% (95% confidence interval [CI] 22–51%) (Table 3). The median duration of response was 10 months. Eleven of 22 (50%) patients with ECOG 0 to 1 responded, but only 5 of 23 with ECOG 2 (21%). There was 1 response among the patients with advanced locoregional disease. With regard to the location of metastases, the response rate was 42% in the liver, 33% in lymph nodes, 33% in the peritoneum, and 11% in the lung. The median overall survival was 9 months (13 months for responders) (Fig. 1).

Table 4 displays the worst toxicity per patient. Gastrointestinal symptoms and anemia predominated. Eleven percent of patients had Grade 3 to 4 nausea/vomiting on at least 1 occasion, 17% diarrhea Grade 3 to 4, 6% stomatitis Grade 3 to 4, and 4% gastric pain Grade 3 to 4. Six patients (13%) had anemia Grade 3 to 4, which was not related to either the presence of a local tumor (only 2 of them) or gastric pain (1/6). Two patients had Grade 3 to 4 neutropenia and 1 of them died of sepsis. This patient also had progressive disease. Except for anemia and alopecia, the other cases of Grade 3 to 4 toxicity appeared just after the first course, and were then avoided with a 25% reduction in the dose of VP-16 and UFT in subsequent courses.

TABLE 4
Worst Toxicity per Patient during the Whole Trial

World Health Organization	Grade 1	Grade 2	Grade 3	Grade 4
Nausea/vomiting	7 (15%)	2 (4%)	4 (9%)	1 (2%)
Diarrhea	6 (13%)	4 (9%)	6 (13%)	2 (4%))
Stomatitis	4 (9%)	4 (9%)	2 (4%)	1 (2%)
Gastric pain[a]	9 (20%)		2 (4%)	
Neutropenia	5 (11%)	2 (4%)	1 (2%)	1 (2%)
Anemia	7 (15%)	3 (6%)	4 (9%)	2 (4%)
Thrombocytopenia	2 (4%)		1 (2%)	
Alopecia	20 (43%)	12 (26%)	5 (11%)	

[a] Gastric pain Grade 1 to 2: it abates with antiacids or H2-blockers. Grade 3 to 4: it is intense enough to require withdrawal of UFT in spite of therapy with antiacids and H2-blockers.

DISCUSSION

Curative therapy for advanced gastric carcinoma is still not available. Even with the better schemes, median survival ranges between 6 and 9 months.[1] Thus, therapy for unresectable gastric cancer remains palliative.

In general, palliative chemotherapy should offer some activity, manageable toxicity, and a reasonable quality of life. The response rate observed in our study is similar to that reported by others who used combinations including 5-FU plus cisplatin and/or anthracyclines.[1,28–30] Although this rate is inferior to that of 53% initially reported with ELF,[2] it is better than the 7% obtained by other investigators who also used ELF.[31] The same happens with FAMTX: although the response rate was 63% initially,[32] a randomized trial achieved a 33% response rate, similar to the one from this study.[33] For this reason, in the absence of direct randomized comparisons among these regimens, we cannot determine the superiority of one regimen over the others.

VP-16-LV-UFT was well tolerated, the main toxicity being digestive. Anemia was the most frequent hematologic toxicity. We do not know why it appears. Although we first related it to chronic tumoral bleeding, there was not evident relation with the presence of a local tumor or the prevalence of gastric pain. No patient received erythropoietin, as it is only approved for cisplatin combinations in Spain. For this reason we do not know whether it could have been of value.

With regard to leukocytes, 20% of patients experienced Grade 3 to 4 leukopenia with the original ELF, but only 4% with our regimen.[2] It appears that the modulation of UFT with LV is less myelotoxic than the modulation of 5-FU,[23,34] hence the interest to combine UFT and LV with other drugs. In spite of this lesser toxicity compared with other schemes,[2,11,29-32] 2 of our patients had Grade 3 to 4 neutropenia and 1 of them died of sepsis.

Oral chemotherapy has two main inconveniences: compliance (patients may take more or fewer pills than scheduled) and absorption. To solve the first problem we need to spend time with the patient to explain the therapeutic plan and the timetable of administration, and to instruct him/her to withdraw medication in the case of serious toxicity. Conversely, previous surgery and the tumor itself could interfere with the absorption and bioavailability of the drug. It has been demonstrated that such a problem does not happen with VP-16.[35] With regard to UFT, pharmacokinetic studies have demonstrated that, after a total gastrectomy, the area under the curve (AUC) of tegafur and uracil does not change. However, after a partial gastrectomy, the AUC of uracil AUC decreases (not that of tegafur). These alterations return to normal 3 months after surgery.[36] For these reasons, limitations in absorption and bioavailability are not likely with VP-16-LV-UFT.

Our experience suggests the feasibility of a predominantly oral scheme of chemotherapy with VP-16, LV, and UFT in patients with advanced gastric carcinoma. This kind of administration avoids hospitalization and the use of infusion pumps, which should decrease the cost of therapy. This consideration along with its efficacy, moderate toxicity, and easy administration lead us to consider that VP-16-LV-UFT is adequate for the ambulatory treatment of patients with advanced gastric carcinoma. Currently we are performing a Phase II trial with the combination Epirubicin-UFT-LV in an attempt to further improve the results of the present study.

REFERENCES

1. Findlay M, Cunningham D. Chemotherapy of carcinoma of the stomach. *Cancer Treat Rev* 1993;19:29–44.
2. Wilke H, Preusser P, Fink U, Achterrath W, Meyer HJ, Stahl M, et al. New developments in the treatment of gastric carcinoma. *Semin Oncol* 1990;17:61–70.
3. Wils JA, Klein HO, Wagener DJTh, Bleiberg H, Reis H, Korsten F, et al. Sequential high-dose methotrexate and fluorouracil combined with doxorubicin - A step ahead in the treatment of advanced gastric cancer: a trial of the EORTC Gastrointestinal Tract Cooperative Group. *J Clin Oncol* 1991;9:827–31.
4. Lacave AJ, Barón FJ, Antón LM, Estrada E, De Sande LM, Palacio I, et al. Combination chemotherapy with cisplatin and 5-fluorouracil 5-day infusion in the therapy of advanced gastric cancer: a phase II trial. *Ann Oncol* 1991;2:751–4.
5. Mahjoubi M, Rougier P, Drozz J, Cvitkovic E, Tigaud JM, Lasser PH, et al. Phase II trial with 5-FU, leucovorin, epirubicin and cisplatinum (FLEP) in advanced gastric adenocarcinoma. *Proc Am Assoc Cancer Res* 1991;32:1103.
6. Pyrhönen S, Kuitunen T, Kouri M. A randomised phase III trial comparing fluorouracil, epidoxorubicin and methotrexate (FAMtx) with best supportive care in non-resectable gastric cancer. *Ann Oncol* 1992;3(Suppl 5):47.
7. Murad AM, Santiago FF, Petroianu A, Rocha PR, Rodrigues MA, Raush M, et al. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. *Cancer* 1993;72:37–41.
8. Berenberg JL, Goodman PJ, Olshi N, Fleming T, Natake RB, Hutchins LH, et al. 5-Fluorouracil (5FU) and folinic acid (FA) for the treatment of metastatic gastric cancer [abstract]. *Proc Am Soc Clin Oncol* 1989;8:101.
9. Louvet C, de Gramont A, Demuynck B, Nordlinger B, Maisai JE, Lagadec B, et al. High-dose folinic acid, 5-Fluorouracil bolus and continuous infusion in poor-prognosis patients with advanced measurable gastric cancer. *Ann Oncol* 1991; 2:229–30.
10. Machover D, Goldschmidt E, Chollet P, Metzger G, Zittou J, Marqut J, et al. Treatment of advanced colorectal and gastric adenocarcinomas with 5-fluorouracil and high-dose folinic acid. *J Clin Oncol* 1986;4:685–96.
11. Moynihan T, Hansen R, Anderson T, Quebbeman E, Beaty P, Ausman R, et al. Continuous 5-fluorouracil infusion in advanced gastric carcinoma. *Am J Clin Oncol* 1988;11:461–4.
12. Findlay M, Cunningham D, Norman A, Mansi J, Nicolson M, Hickish T, et al. A phase II study in advanced gastric cancer using epirubicin and cisplatin in combination with continuous infusion 5-fluorouracil (ECF). *Ann Oncol* 1994;9:805–12.
13. Fujii S, Ikenaka K, Fakushima M, Shirasak T. Effect of uracil and its derivatives on antitumor activity of clinical doses of 1-(2-tetrahydrofuryl)-5-fluorouracil. *Gann* 1978;69:763–72.
14. Fujii S, Kitano S, Ikenaka K, Shirasak T. Effect of coadministration of uracil or cytosine on the antitumour activity of clinical doses of 1-(2-tetrahydrofuryl)-5-fluorouracil and level of 5 fluorouracil in rodents. *Gann* 1979;70:209–14.
15. Taguchi T, Nakano Y, Jikuya. Determination of 5-fluorouracil levels in tumours, blood and other tissues. *Cancer Chemother* 1978;5:1167–72.
16. Cao S, Frank C, Shirasaka T, Rustum YM. 5-Fluorouracil prodrug: role of anabolic and catabolic pathway modulation in therapy of colorectal cancer. *Clin Cancer Res* 1995;1:839–45.
17. Namatame K, Sasaki E, Ko Y, Shimada K, Takahashi H, Nakano H, et al. A double-blind comparison of plasma FUra concentrations after oral administration of UFT and continuous intravenous infusion of FU. *Jpn J Cancer Chemother* 1993;20:2417–9.
18. Palmeri S, Gebbia V, Russo A, Amata MG, Gebbia N, Rausa L. Oral tegafur in the treatment of gastrointestinal tract cancer: a phase II study. *Br J Cancer* 1990;61:475–8.
19. Bjerkeset T, Fjosne HE. Comparison of oral ftorafur and intravenous 5-fluorouracil in patients with advanced cancer of the stomach, colon or rectum. *Oncology* 1986;43:212–5.
20. Fujimoto S, Akao T, Itoh B, Koshizuka I, Koyano K, Kitsukowa Y. Protracted oral chemotherapy with fluorinated pyrimidines as an adjuvant to surgical treatment for stomach cancer. *Ann Surg* 1977;185:462–6.

21. González-Barón M, Feliu J, Ordóñez A, Colmenarejo A, Espinosa E, Zamora P, et al. Phase I study of UFT plus leucovorin in advanced colorectal cancer: a double modulation proposal. *Anticancer Res* 1993;13:759–62.
22. Schilsky RL, Choi KE, Vokes EE, Guaspari A, Guarnieri C, Whalings S, et al. Clinical pharmacology of the steroisomers of leucovorin during repeated oral dosing. *Cancer* 1989;63: 1018–21.
23. González Barón M, Feliu J, de la Gándara I, Colmenarejo A, Jalón JI, Chacón JI, et al. Phase II trial of uracil-tegafur (UFT) and leucovorin (LV) in advanced colorectal cancer [abstract]. *Proc Am Soc Clin Oncol* 1994;13:204.
24. González-Barón M, Feliu J, de la Gándara I, Espinosa E, Colmenarejo A, Martinez-Martínez B, et al. Efficacy of oral tegafur modulation by uracil (UFT) and leucovorin in advanced colorectal cancer. A phase II study. *Eur J Cancer.* In press.
25. Osswalt H, Kunz W. Therapeutic synergism of etoposide and 5-fluorouracil combined sequentially in advanced leukemia L1210 [abstract]. *J Cancer Res Clin Oncol* 1987;115:53.
26. Zubrod C, Schneiderman M, Frei J. Appraisal of methods for the study of chemotherapy of cancer in man: comparative therapeutic trial of nitrogen mustard and thiethylene thiophosphoraminde. *J Chron Dis* 1960;11:7–33.
27. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981;42:207–14.
28. Cervantes A, Villar-Grimalt A, Abad A, Antón-Torres A, Belón J, Dorta J, et al. 5-Fluorouracil, folinic acid, epidoxorubicin and cisplatin (FLEP) combination chemotherapy in advanced measurable gastric cancer. A phase II trial of the Spanish Cooperative Group for Gastrointestinal Tumor Therapy (TTD). *Ann Oncol* 1993;4:753–7.
29. Lerner A, Gonin R, Steele GD, Mayer RJ. Etoposide, doxorubicin and cisplatin chemotherapy for advanced gastric adenocarcinoma: results of a phase II trial. *J Clin Oncol* 1992;10:536–40.
30. González-Barón M, Feliu J, Espinosa E, García-Girón C, Chacón I, Garrido P, et al. FLEP (5-fluorouracil, leucovorin, etoposide, cisplatin) in advanced gastric cancer. *Eur J Cancer* 1994;30:1733–4.
31. Taal BG, Teller FGM, ten Bokkel WW, Boot H, Beijnen JH, Dubbelman R. Etoposide, Leucovorin, 5-Fluorouracil (ELF) combination chemotherapy for advanced gastric cancer: experience with two treatment schedules incorporating intravenous or oral etoposide. *Ann Oncol* 1994;5:90–2.
32. Klein HO, Wickramanayake PD, Dieterle F, Mohr R, Oerkermann H, Gross R. High-dose MTX/5-FU and adriamycin for gastric cancer. *Semin Oncol* 1983;10(Suppl 2):29–31.
33. Kelsen D, Atiq OT, Saltz L, Niedzwiecki D, Ginn D, Chapman D, et al. FAMTX versus etoposide, doxorubicin and cisplatin: a random assignment trial in gastric cancer. *J Clin Oncol* 1992;10:541–8.
34. Pazdur R, Lassere Y, Rhodes V, Ajani JA, Sugarman SM, Patt YZ, et al. Phase II trial of uracil and tegafur plus oral leucovorin: an effective oral regimen in the treatment of metastatic colorectal carcinoma. *J Clin Oncol* 1994;12:2296–300.
35. Taal BG, Beijnen JH, Teller FGM, ten Bokkel WW, Dubbelman R, Boot H. Bioavailability of oral etoposide in gastric cancer. *Eur J Cancer* 1994;30:420–2.
36. Maehara Y, Takeuchi H, Oshiro T, Takahashi I, Inutsuka S, Baba H, et al. Effect of gastrectomy on the pharmacokinetics of tegafur, uracil, and 5-fluorouracil after oral administration of a 1:4 tegafur and uracil combination. *Cancer Chemother Pharmacol* 1994;33:445–9.