Phase II study of UFT and oxaliplatin in first-line treatment of advanced colorectal cancer

The purpose of this study was to evaluate the efficacy, assessed as response rate, and toxicity of UFT (Tegafur-Uracil) in combination with oxaliplatin as first-line treatment of advanced colorectal cancer (CRC). In all, 84 patients with recurrent or metastatic CRC with measurable disease were included. Treatment consisted of oxaliplatin 85 mg m$^{-2}$ in 120-min intravenous (i.v.) infusion on days 1 and 15; i.v. leucovorin (LV) 250 mg m$^{-2}$ given in 2 h on day 1, followed by oral UFT 390 mg m$^{-2}$ on days 1–14, and oral LV 7.5 mg/12 h on days 2–14. Cycles were repeated every 28 days. A total of 492 cycles of chemotherapy were delivered with a median of six per patient (range 1–12). There was one complete response (1%) and 28 partial responses (34%) for an overall response rate of 35% (95% confidence interval (CI); 24–46%). A total of 36 patients (44%) had stable disease, whereas 17 (21%) had a progression. The median time to progression was 7.3 months and the median overall survival was 16.8 months. A prescheduled preliminary analysis was performed after inclusion of 16 patients who detected a high gastrointestinal toxicity, which led to a reduction of the UFT dose to 300 mg m$^{-2}$. With this new dosage, grade 3–4 diarrhoea and grade 3–4 nausea/vomiting dropped to 21 and 14% of patients, respectively. Other grade 3–4 toxicities were stomatitis in one (1%), anaemia in three (5%), neutropenia in two (3%), thrombocytopenia in one (1%), fatigue in six (9%), peripheral sensory neuropathy in nine (14%) and laryngopharyngeal dysesthesia in two patients (2%). The combination of oxaliplatin and UFT–LV is an active, easy-to-administer regimen with moderate toxicity. Hence, this regimen is worthy of further investigation.

British Journal of Cancer (2004) 91, 1758–1762. doi:10.1038/sj.bjc.6602217 www.bjcancer.com
Published online 26 October 2004
© 2004 Cancer Research UK

Keywords: colorectal cancer; chemotherapy; UFT; oxaliplatin; leucovorin

Although 5-fluorouracil (5FU) was developed approximately 50 years ago, it is still an essential part of advanced colorectal cancer (CRC) treatment. It is currently accepted that 5FU continuous infusion and biochemical modulation with leucovorin (LV) increase response rates and time to progression compared to schemas with bolus administration (Advanced Colorectal Meta-Analysis Project, 1992; Meta-Analysis Group in Cancer, 1998a). They also have a more favourable toxicity profile (Meta-Analysis Group in Cancer, 1998b).

Over the last 10 years, significant activity has been observed with other cytotoxics, such as irinotecan (CPT-11) and oxaliplatin, in monotherapy treatment of this tumour type. The addition of oxaliplatin or CPT-11 to 5FU–LV in randomised Phase III trials has shown high antitumoral activity in patients with advanced CRC (de Gramont et al, 2000; Douillard et al, 2000; Giaquetti et al, 2000; Saltz et al, 2000).

Although combined therapy has been an important development in the treatment of advanced CRC, these schemes do have some disadvantages. Firstly, their increased toxicity, particularly when CPT-11 is combined with bolus 5FU–LV (Ledermann et al, 2001; Rothenberg et al, 2001). Secondly, continuous-infusion-based regimens require the use of implantable access devices and portable infusion pumps. In addition to the potential risk of catheter-related complications, this type of regimen can restrict patient activity, which can have a negative effect on their quality of life. For this reason, oral chemotherapy may represent a convenient and more acceptable treatment modality. Besides, some studies indicate that patients prefer oral rather than intravenous (i.v.) therapy, provided that efficacy remains the same (Liu et al, 1997; Borner et al, 2002).

UFT is an oral combination of uracil and tegafur in a molar ratio of 4:1. Tegafur is a prodrug that is metabolised into 5FU by hepatic microsomal cytochrome P450 enzymes or by ubiquitous cytosolic enzymes. Uracil inhibits the catalysis of 5FU by competitive inhibition of the enzyme dihydropyrimidine-dehydrogenase, which maintains active drug levels for a prolonged period and thus simulates a continuous infusion of 5FU. The plasma half-life is of 5–12 h (Fujii et al, 1979; Eng et al, 2001). In a pharmacokinetic study, UFT 370 mg m$^{-2}$ given orally on a 28-day schedule resulted in blood concentrations comparable to those following a continuous i.v. infusion of 5FU 250 mg m$^{-2}$ (Ho et al,
1998). Two Phase III studies have been conducted to compare the efficacy and toxicity of modulation of UFT and LV with SFU–LV (Carmichael et al, 2002; Douillard et al, 2002). Response rate and overall survival were similar, although a slight disadvantage in time to progression was observed for UFT–LV in one of the studies (3.8 vs 3.5 months; \( P < 0.05 \)) (Douillard et al, 2002). However, if we take these studies as a whole, it is acceptable to say that they are equivalent in efficacy and that UFT–LV has a more favourable toxicity profile, with less neutropenia, diarrhoea, nausea/vomiting and mucositis (Mayer, 2001).

Some years ago, we developed a therapeutic scheme to modulate UFT with LV. It consisted of the infusion of a high dose of LV, followed by the oral administration of both UFT and LV for 14 days.

A Phase I trial determined that the maximum-tolerated dose of UFT when modulated in this way was 390 mg m\(^{-2}\) day\(^{-1}\) (González-Barón et al, 1993). This regimen obtained a 39% response rate in patients with advanced colon cancer, both adults (González-Barón et al, 1995) and elderly patients (Feliu et al, 1997).

Oxaliplatin is a third-generation platinum compound that has synergistic antitumour activity with 5FU (Raymond et al, 1997). This synergistic activity is also observed when oxaliplatin is combined with UFT–LV (Louvet et al, 2000).

Therefore, in the light of the above, it is to be expected that the combination of oxaliplatin–UFT–LV will be at least as effective as the combination of oxaliplatin–SFU–LV, although the former could offer greater comfort for patients and a lower toxicity.

The purpose of this multicentre Phase II study is to assess the efficacy (in terms of response rate) and safety of the oxaliplatin–UFT–LV combination as first-line treatment in patients with advanced CRC.

PATIENTS AND METHODS

Patient population

A total of 84 patients with recurrent or metastatic CRC were included from April 1999 to January 2000. They all had at least one lesion histologically or cytologically confirmed adenocarcinoma. Patients who had received prior adjuvant 5FU-based chemotherapy were eligible if they had remained free of disease for at least 6 months after completion of the adjuvant therapy. Patients with operable metastatic disease were excluded from the study. Other inclusion criteria were: (1) a performance status \( \leq 2 \), according to Eastern Cooperative Oncology Group (ECOG) scale. (2) Life expectancy of at least 3 months. (3) Adequate bone marrow function, that is, a granulocyte count \( \geq 2 \times 10^9 \text{l}^{-1} \) and platelets \( > 100 \times 10^9 \text{l}^{-1} \). (4) Adequate hepatic function, that is, serum bilirubin \( < 1.25 \text{ times the upper normal limit, glutamic oxaloacetic transaminase values (SGOT) and glutamic pyruvic transaminases (SGPT) < 2.5 times the upper normal limit in the absence of hepatic metastases or < 3 times the upper normal limit in the presence of metastasis.} \) (5) Adequate renal function, that is, a creatinine value \( \leq 1.25 \text{ times the upper normal limit.} \)

Patients with any prior chemotherapy for advanced disease, brain or meningeal metastases, or a history of any other malignancy were excluded, except in cases of basal cell carcinoma or in situ cervical carcinoma adequately treated. Patients provided written informed consent according to directives of local ethical committees.

All patients had measurable disease, as defined by the presence of at least one bidimensionally measurable lesion by computed tomography scan. Pleural effusion, ascites, osteoblastic lesions or previously irradiated lesions were not accepted as measurable disease. Patients who had received radiotherapy were eligible if there was at least one measurable lesion outside the radiation field.

Treatment plan

The study regimen consisted of oxaliplatin 85 mg m\(^{-2}\) in 120-min i.v. infusion in 250 ml of dextrose 5% on days 1 and 15; i.v. l,LV 250 mg m\(^{-2}\) given over 2 h on day 1, followed by oral UFT 390 mg m\(^{-2}\) on days 1–14; and oral l,LV 7.5 mg 12 h\(^{-1}\) on days 2–14, followed by 2 weeks of rest. An entire course lasted 4 weeks. Pills were taken before meals to favour absorption (for instance, at 0800 and 2000). For practical reasons, UFT doses were rounded up or down to the nearest dose that could be administered with 100 mg capsules of the drug. Routine antiemetic prophylaxis with a 5-hydroxtryptamine-3-receptor antagonist was used. Courses were repeated every 28 days with a minimum of three per patient, unless progressive disease was detected. Responding patients continued therapy until progression or the appearance of unacceptable toxicity.

Patients were assessed for toxicity before each course and graded according to WHO scales (WHO, 1979). Complete blood counts were obtained on days 1 and 14 of each cycle, before each administration of oxaliplatin. Therapy was delayed for 1 week if the neutrophil count was \(< 1.5 \times 10^9 \text{l}^{-1} \) or the platelet count was \(< 100 \times 10^9 \text{l}^{-1} \) or for significant persisting nonhaematologic toxicity. Therapy was discontinued if toxicity persisted after a 2-week delay. In case of grade 3 or 4 haematologic toxicity or any other severe (\( \geq 3 \)) organ toxicity, the dose of all drugs was decreased by 25% in the subsequent cycles. The oxaliplatin dose was reduced by 25% for subsequent cycles in case of persistent (\( \geq 14 \) days) or temporary (7–14 days) painful paresthesia or functional impairment. In case of persistent painful paresthesia or functional impairment, or if a patient experienced any other severe neurotoxicity despite a 25% dose attenuation, oxaliplatin was omitted in subsequent cycles. In case of the occurrence of a laryngeal spasm syndrome, the duration of the oxaliplatin infusion was increased from 2 to 6 h. In case of persistent problems, oxaliplatin was omitted.

Pretreatment and follow-up studies

Patients had a full clinical history, physical examination, performance status assessment, haematological and biochemical profiles (including CEA level), a chest X-ray and a computed tomography scan of the chest and abdomen at baseline. Additional imaging investigations were performed if clinically indicated. A computed tomography scan was repeated every three courses to assess objective response. At the end of chemotherapy, all clinical, laboratory and imaging studies were repeated and patients underwent follow-up examination every 2 or 3 months until death.

Toxicity and response criteria

Toxicity for each course was recorded and graded according to WHO scales (WHO, 1979). For toxicity analysis, the worst data for each patient across all courses were used. Response was evaluated using WHO guidelines (WHO, 1979). A complete response required the total disappearance of all tumours initially observed in two observations not less than 4 weeks apart, with no evidence of new areas of malignant disease. A partial response was defined as a reduction of at least 50% in the sum of the products of the longest perpendicular diameter of all clearly measurable tumour masses, in two observations not less than 4 weeks apart, with no increase in the size of any lesion and no evidence of new lesions. Stable disease was defined as a decrease in total tumour size of less than 50% or a less than 25% increase in any measurable lesion. Progression was defined as a 25% increase in the size of any lesion, the appearance of new areas of malignant disease or performance status deterioration by more than one level. Time to tumour progression was estimated by the product-limit estimation from the date of the first course to the first evidence of disease.
progression. Radiological responses were not evaluated by an Independent Review Committee (IRC). Survival was calculated by the same method from the date of the first course until the date of death or last known follow-up.

Statistical analysis
The primary end point was response rate and the secondary objectives were survival and time to progression. Dose intensity was calculated by dividing the total mg m$^{-2}$ of drug given by the number of weeks elapsed from the beginning of therapy to the end of the last cycle. The sample size was designed to reject a response rate of less than 20%. A total of 19 patients were initially included using the Fleming method (Fleming, 1982). Alternatively, a planned sample size of 80 evaluable patients was chosen to better estimate efficacy; 20% of the maximum width of the 95% confidence interval (CI) for an expected 35% overall response rate. The Wilcoxon's rank-sum method was used to compare quantitative variables, the Fisher's exact test for percentages and the Kaplan–Meier method for survival and the duration of response. Progression-free survival was measured from the start of chemotherapy to the date of progressive disease or death without progression.

RESULTS

Patient characteristics
A total of 84 patients with recurrent or metastatic CRC were included on the study. The characteristics of these patients are shown in Table 1. The median age of the series was 63 years (range 40–77). In total, 47 patients were male (56%) and 37 were female (44%). There were 41 patients (49%) with an ECOG performance status of 0, 37 (44%) with 1 and 6 (7%) with 2. In 52 patients (62%), the primary tumour was located in the colon and in 32 (38%) in the rectum. A total of 22 patients (26%) had previously received chemotherapy as adjuvant therapy and other eight (10%) had received chemotherapy and radiotherapy. The liver was the predominant metastatic site (74%), and the median number of involved sites was two per patient.

Response and survival
Response data are listed in Table 2. One patient (1%) obtained a complete response and 28 (34%) had a partial response, with an overall response rate of 35% (95% CI: 24–46%). A total of 36 patients (44%) had stable disease and 17 (21%) had a progression. The median follow-up for all patients was 14 months. The median duration of response was 7.8 months. The median time to progression was 7.3 months, and the median overall survival 16.8 months. The 1-year actuarial survival rate was 71%.

Toxicity
The first 16 patients received UFT 390 mg m$^{-2}$ day$^{-1}$. Important gastrointestinal toxicity was observed with grade 3–4 diarrhoea in nine patients (56%) and grade 3–4 nausea/vomiting in three (19%). One patient developed grade 3 neutropenia (6%) (Table 3). As a result, the UFT dose was reduced to 300 mg m$^{-2}$ in subsequent patients. This reduced dose was administered to 66 patients and the incidence of grade 3–4 diarrhoea and nausea/vomiting dropped to 21 and 14% of patients, respectively. This toxicity appeared preferentially in the first two cycles. Other grade 3–4 toxicities were stomatitis in one patient (1%), anaemia in three (5%), neutropenia in two (3%), thrombocytopenia in one (1%) and fatigue in six (19%). Oxaliplatin-associated peripheral sensory neuropathy was observed in 73% of patients, with grade 3 neurotoxicity occurring in nine (14%) patients. Grade 3–4 laryngopharyngeal dysesthesia was observed in two patients (2%), and could be prevented in the following treatment cycles by prolonging the duration of oxaliplatin infusion.

| Characteristic | No. (%) |
|---------------|---------|
| Age (years) (mean and range) | 63 (40–77) |
| Sex | |
| Male | 47 (56%) |
| Female | 37 (44%) |
| ECOG performance status | |
| 0 | 41 (49%) |
| 1 | 37 (44%) |
| 2 | 6 (7%) |
| Primary site | |
| Colon | 52 (62%) |
| Rectum | 32 (38%) |
| Metastasis sites | |
| Liver | 62 (74%) |
| Lung | 25 (30%) |
| Local abdominal mass | 16 (19%) |
| Others | 19 (23%) |
| No. of metastatic sites | |
| 1 | 47 (56%) |
| 2 | 32 (38%) |
| ≥3 | 5 (6%) |
| Adjuvant chemotherapy | |
| Yes | 30 (36%) |
| No | 54 (64%) |

| Results | No. of patients (%) |
|---------|---------------------|
| Complete response | 1 (1%) |
| Partial response | 28 (34%) |
| Stable disease | 36 (44%) |
| Progressive disease | 17 (21%) |

Overall response 35% (95% CI: 24–46%).
DISCUSSION

Advanced CRC is currently an incurable disease. Therefore, the objective of treatment must be to prolong survival, obtain effective control of symptoms and maintain or improve quality of life. These objectives should be achieved with an acceptable level of toxicity that does not deteriorate the patient's quality of life.

At present, many treatments used in advanced CRC are based on continuous infusion of 5FU modulated by LV, combined with oxaliplatin or CPT-11. However, continuous infusions require an indwelling central venous catheter, which is a potential risk for infection and thrombosis. Moreover, continuous infusions increase treatment costs and probably reduce patient quality of life. Therefore, the development of schemes with oral fluoropyrimidines that can replace 5FU continuous infusion effectively is an area of research to pursue given the potential enhanced convenience and cost benefits. The aims of our study were to obtain the same therapeutic results as 5FU–LV–oxaliplatin, but with greater convenience for the patient by avoiding the use of infusion pumps. The results obtained show that the combination UFT–l,LV–oxaliplatin is relatively effective in advanced CRC, with overall response rates of 35% and a median survival rate of 16.8 months. Although the response rate is somewhat lower than the 45–60% response rate reported with other oxaliplatin–5FU–LV schemes in first-line therapy of advanced CRC (Bertheault-Cvitkovik et al., 1996; de Gramont et al., 2000; Goldberg et al., 2003), it does not differ significantly from those reported in different Phase II studies with oxaliplatin–capecitabine (31–55%) (Shields et al., 2002; Makatsoris et al., 2003; Tabernero et al., 2003; Zeuli et al., 2003). On the other hand, time to progression and median survival rate are similar to those obtained with these combinations (Bertheault-Cvitkovik et al., 1996; de Gramont et al., 2000; Giacchetti et al., 2000; Shields et al., 2002; Louvet and de Gramont, 2003; Makatsoris et al., 2003; Simpson et al., 2003; Tabernero et al., 2003; Zeuli et al., 2003). Notwithstanding, it can be mentioned that radiological responses were not reviewed by an IRC, and this could have overestimated our results.

In all events, in the absence of Phase III trials with which we can compare these schemes directly, we should use these comparisons with caution.

With regard to toxicity, we should point out the high levels of gastrointestinal toxicity obtained with the initially planned dose of UFT 390 mg m⁻², as 56% of the patients who received this dose developed some form of grade 3–4 toxicity. After reducing the UFT dose to 300 mg m⁻² in the subsequent patients, the incidence of grade 3–4 diarrhea fell to 21% of patients and grade 3–4 nausea and vomiting to 14%. These figures are similar to those reported with 5FU–LV–oxaliplatin schemes (Simson et al., 2003), although the latter reported a higher frequency of grade 3–4 neutropenia (41–48% of patients) (de Gramont et al., 2000; Giacchetti et al., 2000) than that detected in our study (3%).

Relatively few authors have investigated the combination of oxaliplatin–UFT with or without LV, in comparison to the association of oxaliplatin–capecitabine. In a Phase II study on 34 patients previously treated with a fluoropyrimidine-based regimen, oxaliplatin 130 mg m⁻² was administered every 21 days with UFT doses of 350 mg m⁻² for 21 days, without modulation by LV. The response rate was 13% and grade 3–4 toxicity was exceptional, with just one episode of Grade 3 neutropenia (Kim et al., 2002). In another Phase II trial that included 64 patients, oxaliplatin 130 mg m⁻² was administered with UFT (300 mg m⁻²) for 2 weeks, modulated by LV. An overall response rate of 34% and a median time to progression of 5.9 months were obtained, with 12% of patients developing grade 3–4 neutropenia, 11% grade 3 diarrhea and 8% suffering from grade 3 nausea/vomiting (Douillard et al., 2004). These data coincide with what we have observed in our series.

We could conclude by saying that the results of our study suggest that UFT/LV and oxaliplatin can be combined safely. The recommended dose for future studies is UFT 300 mg m⁻², days 1–14, l,LV 250 mg m⁻² i.v. on day 1, LV 15 mg day⁻¹, days 2–14 and oxaliplatin 85 mg m⁻² on days 1 and 14, with repeat treatments every 4 weeks. This is an active scheme with a 35% response rate and a median survival of 16.5 months. It has acceptable toxicity and offers the advantage of convenience with its oral administration. Hence, this regimen is worthy of further investigation.

REFERENCES

Advanced Colorectal Meta-Analysis Project (1992) Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. J Clin Oncol 10: 896–903
Bertheault-Cvitkovik F, Jami A, Ithazki M, Brummer PD, Brienza S, Adam R, Kustlinger F, Bismuth H, Misset JL, Levi F (1996) Biweekly intensified ambulatory chronomodulated chemotherapy with oxaliplatin, fluorouracil, and leucovorin in patients with metastatic colorectal cancer. J Clin Oncol 14: 2950–2958
Borner MM, Schöffski P, de Wit R, Caponigro F, Comella G, Sulkes A, Greim G, Peters GJ, van der Born K, Wanders J, de Boer RF, Martin C, Fumoleau P (2002) Patient preference and pharmacokinetics of oral modulated UFT versus intravenous fluorouracil and leucovorin: a
randomised crossover trial in advanced colorectal cancer. Eur J Cancer 38: 349 – 358

Carmichael J, Popiela T, Radstone D, Falk S, Borner M, Oca A, Skovgaard T, Munier S, Martin C (2002) Randomized comparative study of tegafur/uracil and oral leucovorin in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 20: 3617 – 3627

De Gramont A, Figer A, Seymour M, Homeri M, Hmissi A, Cassidy J, Boni C, Cortes-Funes H, Cervantes A, Freyger G, Papamichail D, Le Bail N, Louvet C, Hendler D, Braud F, Wilson C, Morvan F, Bonetti A (2000) Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 18: 2938 – 2947

Douillard JY, Bennoua J, Artru P, Perrier H, Paillot B, Hussein F, Priou F, Imadalous D, Kelord JP, Bugat R (2004) UFT/LV combination based regimens with oxaliplatin or irinotecan as first-line treatment for patients (pts) with non respectable metastatic colorectal cancer (MCRC): results of two multicentric phase II trials. Proc Am Soc Clin Oncol 23: 256 (abstr. 3545)

Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, Jandik P, Iveson T, Carmichael J, Alakl M, Gruia A, Awad L, Rougier P (2000) Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet 355: 1041 – 1047

Douillard J-Y, Hoff PM, Skillings JR, Eisenberg P, Davidson N, Harper P, Vincent MD, Lembersky BC, Thompson S, Maniero A, Benner SE (2002) Multicenter phase III study of uracil/tegafur and oral leucovorin versus fluorouracil and leucovorin in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 20: 3605 – 3616

Eng C, Kindler HL, Schilsky RL (2001) Oral fluoropyrimidine treatment of colorectal cancer. Clin Colorectal Cancer 1: 95 – 103

Feliu J, González Barón M, Espinosa E, García Girón C, de la Gandara I, Espinosa J, Colmenero A, Jálon JI, Fernández Y, de Castro J (1997) Uracil and tegafur modulated with leucovorin. An effective regimen with low toxicity for the treatment of colorectal carcinoma in the elderly. Cancer 79: 1884 – 1889

Fleming TR (1982) One-sample multiple testing procedure for phase II clinical trials. Biometrics 38: 143 – 151

Fujii S, Kitano S, Irenaka K, Shirasak T (1979) Studies on coadministration of uracilplatin or irinotecan or fluorouracil and the thymidylate synthase inhibitor FTC-207 or 5-FU derivatives. Jpn J Cancer Chemother 6: 377 – 384

Giacchetti S, Perpoint B, Zidani R, Le Bail N, Faggiuolo R, Focan C, Chollet F, Fleming TR (1982) One-sample multiple testing procedure for phase II clinical trials. Anticancer Drugs 13: 387 – 392

Giachetti S, Perpoint B, Zidani R, Le Bail N, Faggiuolo R, Focan C, Chollet F, Fleming TR (1982) One-sample multiple testing procedure for phase II clinical trials. Anticancer Drugs 13: 387 – 392

Goldberg R, Morton R, Sargent D, Fuchs C, Ramathan RK, Williamson SK, Findley BP (2003) N9741: oxaliplatin or CPT-11+5-fluorouracil/leucovorin or oxa+CPT-11 in advanced colorectal cancer. Updated efficacy and quality of life data from an intergroup study. Proc Am Soc Clin Oncol 22: 252 (abstr. 1009)

González Barón M, Feliu J, de la Gandara I, Espinosa E, Colmenero A, Martínez B, Blanco E, García Girón C, Juárez F, Garrido P, Ordóñez A, Zamora P (1995) Efficacy of oral tegafur modulation by uracil (UFT) and leucovorin as first-line treatment of metastatic colorectal cancer. Jpn J Cancer Chemother 22: 360 (abstr. 1447)

Mayer RJ (2001) Oral versus intravenous fluoropyrimidines for advanced colorectal cancer: by either route, it’s all the same. J Clin Oncol 19: 4093 – 4096

Meta-Analysis Group in Cancer (1998a) Efficacy of intravenous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. J Clin Oncol 16: 301 – 308

Meta-Analysis Group in Cancer (1998b) Toxicity of fluorouracil in patients with advanced colorectal cancer: effect of administration schedule and prognostic factors. J Clin Oncol 16: 3537 – 3541

Raymond E, Buguet-Fagot C, Djelloul S, Mester J, Cvitkovic E, allain P, Louvet C, Gespach C (1997) Antitumor activity of oxaliplatin in combination with 5-fluorouracil and the thymidylate synthase inhibitor A337 in human colon, breast and ovarian cancer. Anticancer Drugs 8: 876 – 885

Rothenberg ML, Meropol NJ, Poplin EA, Van Cutsem E, Wandler S (2001) Mortality associated with irinotecan plus bolus fluorouracil/leucovorin: summary findings of an independent panel. J Clin Oncol 19: 3801 – 3807

Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, Maroun JA, Ackland SP, Locker PK, Pirootta N, Elfring GL, Miller LL (2000) Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. N Engl J Med 343: 905 – 914

Shepherd AF, ZhalaPSki MM, Marshall JL, Meropol NJ (2002) A phase II trial of oxaliplatin and capecitabine in patients with advanced colorectal cancer. Proc Am Soc Clin Oncol 21: 143 (abstr. 568)

Simpson D, Dunn C, Curren M, Goa KL (2003) Oxaliplatin. A review of its use in combination therapy for advanced metastatic colorectal cancer. Drugs 63: 2127 – 2156

Tabernero J, Butts CA, Cassidy J, Conroy T, de Braud F, Diaz-Rubio E, Figer A, Schoeffski P, Grossmann J, Sobero A, Twelves C, Van Cutsem E (2003) Capecitabine and oxaliplatin in combination (Xelox), as first line therapy for patients (pts) with metastatic colorectal cancer (MCRC): results of an international phase II trial. Proc Am Soc Clin Oncol 21: 133 (abstr. 531)

World Health Organization 1979 WHO Handbook for Reporting Results of Cancer Treatment WHO offset publication no. 48. Geneva, Switzerland: WHO

Zeuli M, Nardon C, Pino MS, Gamucci T, Gabriele A, Ferraresi V, Giannarelli D, Cognetti F (2003) Phase II study of capecitabine and oxaliplatin as first-line treatment in advanced colorectal cancer. Ann Oncol 14: 1378 – 1382