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Gemcitabine and Protracted 5-Fluorouracil Infusion as Third-line Chemotherapy in Refractory Colorectal Cancer Patients

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Abstract. *Background: There is no standard treatment for patients with advanced colorectal cancer (CRC) progressing after irinotecan and oxaliplatin treatment and having good performance status (PS). Patients and Methods: We investigated gemcitabine 1,000 mg/m^2 days 1, 8 and 15 q28d combined with protracted 5-fluorouracil continuous infusion at 200 mg/m^2/day, in 37 consecutive patients progressing after oxaliplatin-irinotecan-containing chemotherapies. Results: Partial response (PR) was achieved in 4 (10.8%) and disease stabilization (SD) in 19 (51.4%) cases (PR+SD: 62.2%). Median time to progression and survival were 4.2 and 8.9 months, respectively. Grade III toxicities were thrombocytopenia, neutropenia (in 3 patients) and mucositis (in 2 patients). Clinical benefit was observed in 18 patients (48.6% of the entire population; 64.3% of those patients with PS>0 at study entry). Conclusion: The combination of gemcitabine and 5-fluorouracil continuous infusion was found to be an active and manageable palliative regimen for heavily pre-treated patients with metastatic CRC.*

Colorectal cancer (CRC) is the second leading cause of cancer death in Western countries (1). Approximately 30% of all patients with CRC have metastases at diagnosis and 50% of early-stage patients will develop advanced disease (2).

5-Fluorouracil (5FU), usually modulated by folinic acid, represented the mainstay treatment for patients with advanced CRC for a long period. Response rates, however, were low (10-20%) and overall median survival did not exceed one year. Mainly owing to the introduction of irinotecan and oxaliplatin in the past decade, the median duration of survival among patients with advanced disease has increased from 12 to more than 20 months. This figure has further been improved very recently by the introduction of the new biological target-specific agents bevacizumab and cetuximab (3).

While a number of treatments are available for treating patients in first- and second-line settings, today there are no standard therapeutic options for those patients in good performance status whose tumour is resistant to oxaliplatin and irinotecan. Several phase II studies explored the role of different single agents or combination chemotherapy (4-10). These studies, which enrolled selected patients (*i.e.* those with tumours sensitive to chemotherapy), demonstrated that this patient subgroup, experiencing a progression after a second-line treatment, had a median life expectancy of at least 6 months. It is important, then, to continue exploring whether new agents or new combination therapies might be beneficial to these patients, prolonging time to progression and survival, or at least palliating symptoms.

Gemcitabine is a nucleoside analogue of deoxycytidine in which two fluorine atoms have been inserted into the deoxyribofuranosyl ring. As a prodrug, it is phosphorylated in the cells by deoxycytidine kinase to the main metabolite 2'2'-difluorodexoxycytidine 5'-triphosphate. This metabolite inhibits ribonucleotide reductase, which is responsible for producing the deoxynucleotides required for DNA synthesis and repair. The combination of 5FU and gemcitabine may result in longer stabilization of thymidylate synthase and hence in the enhanced inhibition of DNA synthesis (11).

Experimental data testing the combination of 5FU and gemcitabine confirmed this regimen to be active against CRC cells *in vitro* (12, 13). The combination of these two drugs administered by using different schedules and dosages has also shown a significant antitumour activity in patients with different advanced gastrointestinal carcinomas (14-16), including CRC (17, 18). Combination chemotherapy

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consisting of gemcitabine plus protracted continuous infusion of 5FU has been demonstrated to be a manageable, low-toxicity regimen in several studies including patients with pancreatic or biliary tumours (19-21).

In view of these encouraging results, we tested this schedule in patients with metastatic CRC previously submitted to irinotecan and oxaliplatin-based chemotherapy for advanced disease. The primary aim of the study was to evaluate the activity of the combination regimen expressed as disease control rate (clinical response plus disease stabilisation); secondary aims were tolerability, time to progression, overall survival and clinical benefit.

Patients and Methods

Patients. Patients who had received at least two prior lines of chemotherapy containing irinotecan and oxaliplatin were eligible for this study if they had confirmed progressing adenocarcinoma of the colon or rectum radiologically assessable according to the RECIST criteria of disease response (22). Other eligibility criteria included adequate bone marrow reserve, adequate hepatic and renal function, and an estimated life expectancy of at least 12 weeks. Exclusion criteria were central nervous system (CNS) metastases, second primary malignancies (except *in situ* carcinoma of the cervix or basal cell carcinoma of the skin), any investigational agent administered 1 month before enrolment, or prior exposure to gemcitabine. The study was approved by the local Ethics Committee. Written informed consent was obtained from all patients before starting treatment.

Treatment schedule. Treatment consisted of gemcitabine 1,000 mg/m^2 on days 1, 8, and 15 every 28 days given as a 30 minute infusion; 5FU 200 mg/m^2/day given as a protracted continuous infusion. Dose modifications were performed as follows. In cases of grade 3 or 4 myelosuppression according to the WHO scale, gemcitabine was withheld and 5FU continued. Gemcitabine was then discontinued until toxicity was fully alleviated (*i.e.* grade 0) in the following programmed chemotherapy day. In cases of two consecutive gemcitabine omissions, its dose was reduced by 25% in the subsequent cycles. 5FU infusion was discontinued until toxicity recovery in cases of severe palmoplantar erythema, grade 3-4 diarrhoea, or grade 3-4 mucositis. In these two latter cases, a 25% dose reduction of 5FU was planned for subsequent cycles.

Relative dose intensity was defined as the actual delivered weekly doses of gemcitabine and 5FU at the end of treatment divided by the planned weekly dose. Supportive care included blood transfusion, administration of analgesics, antiemetics and growth factors as appropriate.

Assessment of response and toxicity. Pretreatment evaluation included medical history and physical examination, complete blood cell count, serum chemistries, electrocardiogram, carcinoembryonic antigen and radiological staging. Clinical monitoring, complete blood tests and toxicity evaluation according to common toxicity criteria (CTC) v.2.0 were performed once weekly.

Antitumour activity was evaluated every 3 months on all measurable lesions according to the RECIST criteria (22); all patients were scheduled for at least a 2-month treatment in order to be eligible for assessment of tumour response. Clinical responses were confirmed at least one month after the first occurrence. In patients with tumour response or stable disease, the treatment was planned to be continued for up to 6 months. After the completion of the treatment plan, patients were monitored every 3 months or at a new symptom appearance.

All deaths and treatment discontinuations were considered as progressive disease. Clinical benefit response was evaluated accordingly to the method proposed by Rothenberg *et al*. (23). Time to progression was calculated from the beginning of cytotoxic chemotherapy until the date of objective evidence of progressive disease (PD). Survival was dated from the first day of treatment until death or was censored on the date of the last follow-up appointment.

Statistical analysis. The primary study end-point was the assessment of the disease control [objective response (OR) + SD]. According to the optimal two-stage phase II study Simon design (24), the sample size was assessed to be 4 responses in the first 16 patients and 16 responses in a total of 33 patients. Time to progression and survival were represented using the Kaplan-Meier method and compared with the Log-rank test. All statistical analyses were performed using the Statistica for Windows software program Ver. 6.0 (Tulsa, OK, USA).

Results

From May 2001 to March 2004, 37 consecutive patients with a median age of 64 years were enrolled. The demographic data, sites of metastatic tumour and prior therapies are listed in Table I. The study population consisted of 26 patients (70.3%) with adenocarcinoma of the colon and 11 patients (29.7%) with adenocarcinoma of the rectum. Liver metastases were found in 26 patients (70.3%), lung metastases were found in 23 (62.2%). Thirty-five patients (94.6%) had undergone radical resection of the primary tumour and 14 patients (37.8%) had undergone metastatic resection after first-line therapy: 10 had hepatectomy, 3 had resection of the lung, and 1 both. Previous chemotherapy lines are listed in Table II. As a whole, the majority of the patients (30/37, 81%) had received oxaliplatin-containing regimens as first-line treatment and 27/37 patients (73%) had received irinotecan-containing regimens as second-line option.

Treatment activity. All registered patients were assessed for response, including 2 patients undergoing early treatment interruption: 1 for allergic reaction and 1 for consent withdrawal; these 2 patients were considered as failures. According to the RECIST criteria, 23 out of 37 cases attained disease control (62.2%), consisting of 4 (10.8%) partial responses and 19 (51.4%) clinical stabilisations, whereas 14 progressed (37.8%). Clinical benefit was observed in 18 patients (48.6% of the entire population; 64.3% of those patients with PS>0 at study entry). At the last follow-up appointment (February 2006), all the patients

Table I. *Patient characteristics*.

	No. of patients	%
Total	37	
Age (years)		
Median (range)	64 (31-75)	
Gender		
Male	25	67.6
Female	12	32.4
Site of tumour		
Colon	26	70.3
Rectum	11	29.7
Performance status*		
0	9	24.3
1	23	62.2
2	4	10.8
3	1	2.7
Stage at first diagnosis		
B1	2	5.4
B2	5	13.5
C1	1	2.7
C2	9	24.3
D	20	54.1
Time to first diagnosis (months)		
Median (range)	27.5 (6-108)	
Sites of metastatic disease		
Liver	26	70.3
Lung	23	62.2
Bone	4	10.8
Abdomen	12	32.4
No. of sites of disease		
1	16	43.2
2	14	37.8
3	7	19.0
Previous therapies:		
Surgery	35	94.6
Radiotherapy	4	10.8
Adjuvant chemotherapy	12	32.4
Surgery of metastasis after therapy	14	37.8
Liver	10	27.0
Lung	3	8.1
Liver + lung	1	2.7

*Eastern Cooperative Oncology Group.

Table II. *Previous chemotherapies*.

	No. patients	%
First-line chemotherapy		
FOLFOX2	8	21.6
CRONO 4/10FFL	22	59.5
CRONO FF	2	5.4
CRONO FFC	3	8.1
FOLFIRI	2	5.4
Second-line chemotherapy		
IRINOTECAN	23	62.2
CRONO 4/10FFL	10	27.0
CRONO FFC	3	8.1
CRONO FFCL	1	2.7

FOLFOX2: oxaliplatin 100 mg/m^2/day, folinic acid 300 mg/m^2/day in 2 h infusion, 5FU 1500-1800 mg/m^2/day in 22 h infusion d1-2 q14d; CRONO 4/ 10FFL: oxaliplatin 25 mg/m^2/day, folinic acid 300 mg/m^2/day, 5FU 700-1000 mg/m^2/day d1-4 *q14d*; CRONO FF: folinic acid 300 mg/m^2/day, 5FU 700-1000 mg/m^2/day d1-4 *q14d*; CRONO FFC: irinotecan 180 mg/m^2/day, folinic acid 300 mg/m^2/day, 5FU 700 mg/m^2/day d2-5 *q14d*; FOLFIRI: irinotecan 180 mg/m^2/day, folinic acid 200 mg/m^2/day 2 h infusion, 5FU 400 mg/m^2/day bolus, 5FU 600 mg/m^2/day 22 h infusion d1-2 *q14d;* IRINOTECAN: 100 mg/m^2/day weekly *3wq4w*; CRONO FFCL: irinotecan 180 mg/m^2/day d1, oxaliplatin 25 mg/m^2/day, folinic acid 300 mg/m^2/day, 5FU 700 mg/m^2/day d2-5 *q21d*.

Table III. *Toxicity per patient*.

	No. patients (%) Grade				
Toxicity	0	1	2	3	4
Leucopenia	15 (40.6)	12 (32.4)	10 (27.0)	0	0
Neutropenia	17 (46.0)	5 (13.5)	12 (32.4)	3 (8.1)	0
Thrombocytopenia	18 (48.7)	10 (27.0)	6 (16.2)	3 (8.1)	0
Nausea/vomiting	25 (67.6)	12 (32.4)	0	0	0
Diarrhoea	24 (64.9)	10 (27.0)	3 (8.1)	0	0
Mucositis	20 (54.1)	12 (32.4)	3 (8.1)	2 (5.4)	0
Fever	18 (48.7)	19 (51.3)	0	0	0

showed disease progression and 36 (97.3%) had died. Median time to progression (TTP3) and overall survival were 4.2 (lower and upper quartiles: 2.9-6.3 months) and 8.9 (lower and upper quartiles: 6.3-12.1) months, respectively. One-year survival was 27.0% (10/33).

Toxicity. A total of 160 cycles of therapy were administered (median: 4 cycles; range: 1-9). Fourteen patients (37.8%) ended the treatment plan (6 cycles or more), 2 (5.4%) received 5 cycles, 10 (27.0%) received 4 cycles, 3 (8.2%) received 3 cycles, 6 (16.2%) received 2 cycles, and 2 (5.4%) received 1 cycle. Associated side-effects are reported in Table III. Leucopenia and thrombocytopenia were the most frequent severe toxicities. Gastrointestinal toxicities included grade 3 mucositis in 2 patients. Nausea/vomiting and diarrhoea were frequent but generally mild. No patients experienced grade 4 toxicities. The dose of gemcitabine was reduced or omitted in 25 patients (69.4%) [104 courses (65.8%)], while the doses of 5FU were reduced or omitted in 13 patients (36.1%) [46 courses (29.1%)].

The median dose intensity for gemcitabine was 500 mg/m^2/wk (66.6% of the planned dose), and the median dose intensity of 5FU was 1,283 mg/m^2/wk (91.6% of the planned dose).

Discussion

The combination of gemcitabine and continuous infusion of 5-fluorouracil as third-line chemotherapy in CRC patients was shown to be a manageable and active regimen permitting disease control and clinical benefit in about two thirds of the recruited patients.

In the last ten years, the introduction of irinotecan, oxaliplatin and, more recently, of new agents targeting the biological structure of the tumour resulted in a significant prolongation of survival. More than 60% of patients progressing after a first-line treatment receive a second-line chemotherapy (25, 26). Thus, it is not rare to manage patients in good performance status with tumours resistant to both irinotecan and oxaliplatin who are eligible for a further treatment line. In the literature, the proportion of patients who are submitted to a third-line therapy with respect to those who received a first-line treatment is not clear. From 1994, we entered all the stage IV patients consecutively submitted in our Institution to a first-line chemotherapy into an electronic database. According to our records, 220 out of 336 patients (65.5%) progressing to a first-line treatment were submitted to a second-line regimen, whereas 79 out of 198 patients (39.9%) progressing to a second-line treatment were submitted to a third-line regimen, representing nearly a quarter of those submitted to a first-line scheme (data not shown). This opens several issues for discussion. Firstly, it is questionable if it is ethical to administer a new chemotherapy regimen with unknown activity in patients already heavily treated with two very efficacious schemes. This should be ascertained in well-designed phase III studies comparing new agents or new combination schemes *versus* best supportive care. Secondly, the choice of study end-points is debatable. The time to "third" progression is highly influenced by the interval between restagings. Ideally, in order to better define median time to progression of less than 6 or even 3 months, the restaging frequency should be planned monthly or even bimonthly, this would seem unethical in this patient setting. Survival is linked to the previously administered treatments. In fact, heavily pretreated patients have less chance of surviving longer than those who received a non-active first- or second-line chemotherapy. This explains the discordant results published in the literature: patients pretreated with 5FU in first-line and irinotecan in second-line setting showed a TTP3 of 5.4 months and a overall survival of 9.3 months after mitomyin-C plus capecitabine (4), whereas the same figures in patients heavily pretreated with both FOLFOX and FOLFIRI regimens were 2.6 and 6.8 months, respectively (5). Finally, responses are generally rare in this patient setting, stabilisation of a previous progressing disease being an optimal goal. Thus, we decided to calculated the sample size of our study according to this specific aim, calculating as 50% the expected proportion of those patients obtaining clinical response or disease stabilisation with the experimental therapy versus a 15% stabilisation rate in a hypothetical control placebo arm.

The total number of planned cycles in our study was 6. This may appear inappropriate since most published clinical trial protocols describe treatment until disease progression or tolerance. However, when we planned the treatment protocol, we considered the time to third progression an important secondary aim to compare our results to those already reported in similar patient setting. Moreover, we felt that patients receiving a third-line regimen might be more "fragile" from a treatment compliance point of view. This was confirmed by our results, in which 14 out of 37 patients (37.8%) completed the treatment plan with a median of administered cycles of 4.

While 5FU dose intensity was near to that planned (91.6%), patients received about two thirds of the designed gemcitabine dose. This was due to myelosuppression that was frequently observed on day 15, often obliging us to withhold gemcitabine administration. The response rate was 10.8% with a disease control rate of 62.2%, a median time to third progression of 4.2 months and a median survival of 8.9 months. These figures compare favourably with those reported in the literature. Considering patients heavily pretreated with 5FU, irinotecan and oxaliplatin, disease control rates and survivals were 33.6% and 5 months with raltitrexed plus mitomycin-C (6), 15% and 6.1 months with capecitabine (7), 23.8% and 6.8 months with capecitabine plus mitomycin-C (5), and 63.6% and 9.8 months with cetuximab plus irinotecan (8), respectively. As a descriptive comparison only, it is interesting that patients in the same setting and submitted to best supportive care alone presented a median survival of about 6 months (9). Moreover, two thirds of our patients obtained a clinical benefit from therapy. Such figures not reported by other authors, in our opinion, represent one of the issues that alone could justify the administration of a third-line therapy in this subset of patients, even in the absence of clear drug activity.

Our data confirmed previous reports on the possible activity of gemcitabine against CRC. On the basis of preclinical studies (12-13), gemcitabine combined with 5FU and folinic acid was tested in a phase I study obtaining a response rate of 38% in pretreated patients (10). More recently, the combination of gemcitabine, 5FU, folinic acid and oxaliplatin as second-line treatment was reported to be well tolerated, with a response rate of 41.5% (17). Finally, gemcitabine plus FOLFOX4 plus interleukin-2 in pretreated patients resulted in a response rate of 68.9% (18). However, despite this encouraging preclinical and clinical evidence, the real role of gemcitabine against CRC needs to be ascertained in specifically designed phase III studies, as we cannot separate its activity from that of well-known agents such as 5FU and oxaliplatin.

Finally, we must take into consideration that in recent years, oxaliplatin, variously combined with biological agents, is being more frequently administered in an adjuvant setting (27-30) and that consequently irinotecan combined with biologicals will represent the first choice in cases of relapse (31). Thus, it can be argued that in the immediate future, we will not have valid second-line treatments and any observations on the possible activity of new agents or combination regimens might be important. In conclusion, the encouraging results of this study could represent the basis for future trials exploring the possible role of gemcitabine in the management of heavily pretreated patients suffering from CRC.

References

1 Gill S, Thomas RR and Goldberg RM: Review article: colorectal cancer chemotherapy. Aliment Pharmacol Ther *18(7)*: 683-692, 2003.

2 Midgley R and Kerr D: Colorectal cancer. Lancet *353(9150)*: 391-399, 1999.

3 Venook A: Critical evaluation of current treatments in metastatic colorectal cancer. Oncologist *10(4)*: 250-261, 2005.

4 Chong G, Dickson JLB, Cunningham D, Norman AR, Rao S, Hill ME, Price TJ, Oates J and Tebbutt N: Capecitabine and mitomycin C as third-line therapy for patients with metastatic colorectal cancer resistant to fluorouracil and irinotecan. Br J Cancer *93(5)*: 510-514, 2005.

5 Lim do H, Park YS, Park BB, Ji SH, Lee J, Park KW, Kang JH, Lee SH, Park JO, Kim K, Kim WS, Jung CW, Im YH, Kang WK and Park K: Mitomycin-C and capecitabine as third-line chemotherapy in patients with advanced colorectal cancer: a phase II study. Cancer Chemother Pharmacol *56(1)*: 10-14, 2005.

6 Rosati G, Rossi A, Germano D, Reggiardo G and Manzione L: Raltitrexed and mitomycin-C as third-line chemotherapy for colorectal cancer after combination regimens including 5-fluorouracil, irinotecan and oxaliplatin: a phase II study. Anticancer Res *23(3C)*: 2981-2985, 2003.

7 Gubanski M, Naucler G, Almerud A, Lideståhl A and Lind PA: Capecitabine as third line therapy in patients with advanced colorectal cancer. Acta Oncol *44(3)*: 236-239, 2005.

8 Vincenzi B, Santini D, Rabitti C, Coppola R, Beomonte Zobel B, Trodella L and Tonini G: Cetuximab and irinotecan as third-line therapy in advanced colorectal cancer patients: a single centre phase II trial. Br J Cancer *94(6)*: 792-797, 2006.

9 Rao S, Cunningham D, De Gramont A, Scheithauer W, Smakal M, Humblet Y, Kourteva G, Iveson T, Andre T, Dostalova J, Illes A, Belly R, Perez-Ruixo JJ, Park YC and Palmer PA: Phase III double-blind placebo-controlled study of farnesyl transferase inhibitor R115777 in patients with refractory advanced colorectal cancer. J Clin Oncol *22(19)*: 3950-3957, 2004.

10 Madajewicz S, Hentschel P, Burns P, Caruso R, Fiore J, Fried M, Malhotra H, Ostrow S, Sugarman S and Viola M: Phase I chemotherapy study of biochemical modulation of folinic acid and fluorouracil by gemcitabine in patients with solid tumor malignancies. J Clin Oncol *18(20)*: 3553-3557, 2000.

11 Plunkett W, Huang P, Searcy CE and Gandhi V: Gemcitabine: preclinical pharmacology and mechanisms of action. Semin Oncol *23(5 Suppl 10)*: 3-15, 1996.

12 Schultz L, Schalhorn A, Wilmanns W and Heinemann V: Synergistic interaction of gemcitabine and 5-fluorouracil in colon cancer cells. Proc. ASCO *17*: 965 abstr, 1998.

13 Tesei A, Ricotti L, De Paola F, Amadori D, Frassineti GL and Zoli W: *In vitro* schedule-dependent interactions between the multitargeted antifolate LY231514 and gemcitabine in human colon adenocarcinoma cell lines. Clin Cancer Res *8(1)*: 233-239, 2002.

14 Berlin JD, Alberti DB, Arzoomanian RZ, Feierabend CA, Simon KJ, Binger KA, Marnocha RM and Wilding G: A phase I study of gemcitabine, 5-fluorouracil and leucovorin in patients with advanced, recurrent, and/or metastatic solid tumors. Invest New Drugs *16(4)*: 325-330, 1998-1999.

15 Kliche KO, Kubsch K, Raida M, Masri-Zada R and Höffken K: Chronomodulated chemotherapy in metastatic gastrointestinal cancer combining 5-FU and sodium folinate with oxaliplatin, irinotecan or gemcitabine: the Jena experience in 79 patients. J Cancer Res Clin Oncol *128(9)*: 516-524, 2002.

16 Correale P, Cerretani D, Clerici M, Messinese S, Marsili S, Petrioli R, Cetta F, Savelli V, Guarnieri A, Pinto E, Giorgi G and Francini G: Gemcitabine (GEM), 5-fluorouracil (5-FU) and folinic acid (FA) in patients with different gastroenteric malignancies. J Chemother *16(2)*: 206-210, 2004.

17 Correale P, Messinese S, Canaglia M, Marsili S, Piccolomini A, Petrioli R, Ceciarini F, Micheli L, Nencini C, Neri A, Vuolo G, Guarnieri A, Abbruzzese A, Prete SD, Giorgi G and Francini G: A novel biweekly multidrug regimen of gemcitabine, oxaliplatin, 5-fluorouracil (5-FU), and folinic acid (FA) in pretreated patients with advanced colorectal carcinoma. Br J Cancer *90*: 1710- 1717, 2004.

18 Correale P, Cusi MG, Tsang KY, Del Vecchio MT, Marsili S, Placa ML, Intrivici C, Aquino A, Micheli L, Nencini C, Ferrari F, Giorgi G, Bonmassar E and Francini G: Chemo-immunotherapy of metastatic colorectal carcinoma with gemcitabine plus FOLFOX 4 followed by subcutaneous granulocyte macrophage colony-stimulating factor and interleukin-2 induces strong immunologic and antitumor activity in metastatic colon cancer patients. J Clin Oncol *23(35)*: 8950-8958, 2005.

19 Knox JJ, Hedley D, Oza A, Siu LL, Pond GR and Moore MJ: Gemcitabine concurrent with continuous infusional 5-fluorouracil in advanced biliary cancers: a review of the Princess Margaret Hospital experience. Ann Oncol *15(5)*: 770-774, 2004.

20 van Riel JM, van Groeningen CJ, Pinedo HM and Giaccone G: Current chemotherapeutic possibilities in pancreaticobiliary cancer. Ann Oncol *10(Suppl 4)*: 157-161, 1999.

21 Cascinu S, Frontini L, Labianca R, Catalano V, Barni S, Graiff C, Picone G, Farinati F, Zonato S, Pessi MA, Curti C and Catalano G: A combination of a fixed dose rate infusion of gemcitabine associated to a bolus 5-fluorouracil in advanced pancreatic cancer, a report from the Italian Group for the Study of Digestive Tract Cancer (GISCAD). Ann Oncol *11(10)*: 1309-1311, 2000.

22 Therasse P, Arbruck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC and Gwyther SG: New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst *92(3)*: 205-216, 2000.

23 Rothenberg ML, Moore MJ, Cripps MC Andersen JS, Portenoy RK, Burriss HA 3rd, Green MR, Tarassoff PG, Brown TD, Casper ES, Storniolo AM and Von Hoff DD: A phase II trial of gemcitabine in patients with 5-FU-refractory pancreas cancer. Ann Oncol *7(4)*: 347-353, 1996.

24 Simon R: Optimal two-stage designs for phase II clinical trials. Control Clin Trials *10(1)*: 1-10, 1989.

25 Tournigand C, André T, Achille E, Lledo G, Flesh M, Mery-Mignard D, Quinaux E, Couteau C, Buyse M, Ganem G, Landi B, Colin P, Louvet C and de Gramont A: FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol *22(2)*: 229-237, 2004.

26 Grothey A, Sargent D, Goldberg RM and Schmoll HJ: Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. J Clin Oncol *22(7)*: 1209-1214, 2004.

27 Chua YJ and Zalcberg JR: Progress and challenges in the adjuvant treatment of stage II and III colon cancers. Expert Rev Anticancer Ther *8(4)*: 595-604, 2008.

28 Taieb J, Puig PL and Bedenne L: Cetuximab plus FOLFOX-4 for fully resected stage III colon carcinoma: scientific background and the ongoing PETACC-8 trial. Expert Rev Anticancer Ther *8(2)*: 183-189, 2008.

29 Labianca R, Milesi L, Mosconi S, Pessi MA, Beretta GD and Quadri A: The role of adjuvant chemotherapy in colon cancer. Surg Oncol *16(Suppl 1)*: S93-96, 2007.

30 Benson AB 3rd: New approaches to assessing and treating early-stage colon and rectal cancers: cooperative group strategies for assessing optimal approaches in early-stage disease. Clin Cancer Res 13(22 Pt 2): 6913s-6920s, 2007.

31 Rodriguez J, Zarate R, Bandres E, Viudez A, Chopitea A, García-Foncillas J and Gil-Bazo I: Combining chemotherapy and targeted therapies in metastatic colorectal cancer. World J Gastroenterol *13(44)*: 5867-5876, 2007.

31 Lee JJ and Chu E: An update on treatment advances for the first-line therapy of metastatic colorectal cancer. Cancer J *13(5)*: 276-281, 2007.

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