

The Efficacy of Gemcitabine as Salvage Treatment in Patients with Refractory Advanced Colorectal Cancer (CRC): A Single Institution Experience

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Abstract. *Objective: To assess the efficacy of gemcitabine based chemotherapy in heavily pre-treated patients with advanced colorectal cancer. Patients and Methods: Patients, who had been treated with gemcitabine 1250-2000 mg/m² biweekly in combination with capecitabine 1700-2000 mg/m²/day, d1-7 every two weeks were retrospectively reviewed. All the patients had previously received at least three chemotherapy regimens and 12 (55%) had also received a 4th line regimen. All the patients had been treated with a monoclonal antibody either against vascular endothelial growth factor receptor (VEGFR) or endothelial growth factor receptor (EGFR) (only if wild-type KRAS). The patients had had blood tests weekly, carcinoembryonic antigen (CEA) level measurement every 4 weeks and radiological assessment of their disease with CT scans every 8/9 weeks. Results: Twenty two patients were included; male-female, 14:8; age ranged from 43-73 years. The majority of the patients (17/22) had performance status (PS) ECOG 0-1 and the remaining patients (5/22) had PS 2 at the time of initiation of the gemcitabine-based regimen. Thirteen patients demonstrated a clinical benefit (2 partial response, 2 minor response, 9 stable disease), 6 patients progressed and 2 were not evaluable. Conclusion: Gemcitabine has a modest activity in heavily pre-treated colorectal cancer patients and may be an option in good performance status patients.*

Colorectal cancer (CRC) is the third commonest cancer diagnosed each year in the UK and in the United States and the second commonest cause of death among all cancer patients (1). The lifetime probability of developing CRC has been estimated

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to be 1 in 18 in men and 1 in 20 in women. At the time of diagnosis, synchronous metastases can be found in about 20% of patients (2, 3) and most patients with stage III or IV disease are likely to relapse within the first three years from diagnosis. Apart from the long existing class of fluoropyrimidines (thymidylate synthase inhibitors such as 5-fluorouracil and capecitabine), other cytotoxic drugs such as oxaliplatin, a third generation DNA cross linking platinum agent, and irinotecan, a topoisomerase-I inhibitor and hemisynthetic analogue of the natural compound camptothecin, are now considered as standard treatment options for advanced CRC (4, 5). There is, also, published evidence that the addition of monoclonal antibodies (cetuximab, panitumumab, bevacizumab), targeting the epidermal growth factor receptor (EGFR) or the vascular endothelial growth factor receptor (VEGFR), to the standard chemotherapy improves efficacy and overall survival in selected patients. When the aforementioned drugs have failed, regardless of the sequence or the combinations that have been used, no standard treatment exists, therefore new drugs need to be tested to expand the current options. Small phase II studies have provided some evidence of efficacy for some of the known cytotoxics in advanced multi-treated CRC patients. For example, the combination of mitomycin C with capecitabine in third line treatment of advanced CRC demonstrated an objective response rate of about 15% as well as disease stabilization of half of the patients (6).

The role of gemcitabine in CRC has not yet been established. Eight studies (two with phase I design and six phase II) evaluating the safety and efficacy of gemcitabine along with a fluoropyrimidine were found and reviewed by Merl *et al.* (7), who concluded that the combination is clinically active as demonstrated by a response rate of 30-38%, time to progression of 4-8.3% and median overall survival of 9.8 to over 18 months, with manageable toxicities. More recently, a randomized phase II study compared FOLFOX 4 (folinic acid, fluorouracil, oxaliplatin) to FFG (folinic acid, 5-fluorouracil, gemcitabine) in the 1st line setting of CRC, with the addition of bevacizumab allowed in both treatment arms after its Food and Drug

Table I. Treatment design and follow up.

	Total patients (pts) number (N)	22
Regimen	1. Gemcitabine (G) 1250-2000mg/m ² <i>i.v.</i> over 30 minutes, every 2 weeks 2. Capecitabine 850-1000 mg/m ² from day 1-7, every 2 weeks	<ul style="list-style-type: none"> • 2 pts: 1250 mg/m² • 8 pts: 1500 mg/m² • 6 pts: 1750 mg/m² • 6 pts: 2000 mg/m²
Laboratory follow up	<ul style="list-style-type: none"> • FBC and biochemistry: weekly • CEA: every 4 weeks • Radiology assessment: CT scans chest-abdomen every 8-9 weeks 	
Supporting treatment	<ul style="list-style-type: none"> • Prophylactic antiemetics for 2 days • Prophylactic Pegfilgrastim in pts on G ≥1500 mg/m² 	

CEA, Carcinoembryonic antigen; CT, computed tomography; FBC, full blood count; *i.v.*, intravenous.

Administration approval (8). Though, the study was closed prematurely due to poor accrual (84 patients enrolled of a planned 190), the authors concluded that gemcitabine has inferior efficacy and cannot replace oxaliplatin in this setting. Nevertheless, given the limited options in heavily pre-treated CRC patients, a drug with acceptable safety profile should be evaluated even if modest activity is expected. Thus, the present study, aimed to provide some evidence on the role of gemcitabine in advanced, pre-treated CRC patients.

Patients and Methods

The efficacy, safety and toxicity data on patients at our institution diagnosed with cytologically or histologically proven metastatic colorectal adenocarcinoma who had been treated with gemcitabine (G) and capecitabine (C) salvage chemotherapy was retrospectively reviewed. According to institutional standards, all these patient had satisfactory bone marrow function (hemoglobin >9 g/dl; absolute neutrophil count >1500 cells/mm³ and platelet count >1000,000 cells/mm³); renal (serum creatine <1.5 mg/dl) and liver function (serum total bilirubin <1.5 mg/dl and serum transaminases <2.5 times the upper limit of laboratory normal) before the administration of GC chemotherapy. The treatment regimen consisted of gemcitabine at doses from 1250-2000 mg/m² *i.v.* infusion over 30 min every 2 weeks and oral (PO) capecitabine 850-1000 mg/m², twice a day, on days 1 to 7 every 2 weeks (Table I). The patients received GC as fourth or fifth- line treatment and continued until disease progression. Pre-emptive antiemetics included ondasetron (Zofron) 8 mg *i.v.* and dexamethasone 10 mg *i.v.* prior to the administration of gemcitabine according to the institutional guidelines. Furthermore, pegfilgrastim support was given prophylactically in patients receiving G ≥1500 mg/m² on day 2 every 2 weeks.

Complete blood, platelet and differential counts and biochemistry profile were performed every two weeks. Toxicity was documented and graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0 (available at the webpage: http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae3.pdf). Serum carcinoembryonic antigen (CEA) levels were measured every 4 weeks and CT scans were performed after

every eight weeks until disease progression. Staging and radiological evaluation was performed according to the Response Evaluation Criteria in Solid Tumors (RECIST) (9). The reference range for CEA in our institution was <3 µg/L in non-smokers and <5 µg/L in smokers. The efficacy in terms of the response rate to the GC combination in heavily pre-treated patients was assessed.

Data was obtained from Electronic Patients Records included age, gender, performance status (PS, ECOG), type of previous chemotherapy regimens, doses of GC regimen and previous biological regimens. CT scan results and RECIST criteria were used for the measurement of response.

Results

Between January 2006 and February 2010, 22 advanced CRC patients had been treated with GC.

The patients' baseline characteristics are shown in Table II. Age ranged from 43 to 73 years and gender ratio (M:F) was 14:8. All the patients had previously received at least three chemotherapy lines and half of them (55%) a fourth line regimen as well. All 22 patients had also received bevacizumab and 70% (15/22) an EGFR inhibitor (cetuximab or panitumumab), while 30% (7/22) were tested mutant for *KRAS* and did not receive an EGFR inhibitor. PS was ECOG 0-1 in 17 patients and ECOG 2 in 5 patients. The median number of treatment cycles was 8 (range 4-14). The patients with PS ECOG 2 or who were ≥70 years of age were treated with the escalation dose schema.

Table III displays the response rates and duration of response (DoR) observed in the 22 treated patients. The disease control rate (DCR) was 59% (13/22) of which 9% was a partial response (PR) and 9% a good response, but not amounting to PR by RECIST. The duration of response for the two patients with PR was 6 months and 7.5 months respectively, and for the patients with a minor response 4 months (16 weeks). The DoR for the patients with stable disease ranged from 2 to 4 months.

Table II. *Baseline characteristics.*

Total patients number	N=22
Male/Female (N)	14/8
Age, Range (Years)	43-73
Performance Status (%) (ECOG)	0-1: 77%
	2: 33%
Number of previous treatment lines (%)	3 (100%)
	4 (55%)
Previous use of targeted agents	Bevacizumab (100%) Cetuximab or Panitumumab (70%)

ECOG, Eastern Cooperative Oncology Group.

Table III. *Treatment outcomes.*

Best response to treatment	Number (%)	Duration of response (months)
Partial response (PR)	2 (9.1)	6-7.5
Minimal response (MR)	2 (9.1)	4
Stable disease (SD)	10 (45.4)	2-4
Disease progression (PD)	6 (27.3)	
Not evaluated	2	
Disease control rate (DCR) (PR+MR+SD)	14 (63.6)	
Cycles of treatment	4-14 (Median:8)	

Discussion

The combination of gemcitabine with capecitabine is well established and often used in advanced pancreatic cancer and less often in cholangiocarcinoma (10, 11). From an early dose escalation study, the combination of gemcitabine and capecitabine was found to be safe, well-tolerated and effective in pancreatic and CRC patients (12). There is evidence that gemcitabine may modify the pharmacokinetic properties of 5-FU, *in vivo*, and result thus in a synergistic effect (13). In a prospective study of gemcitabine in combination with protracted 5-FU infusion, as third line treatment of CRC, disease stabilization was achieved in about 60% of patients (10% of which being partial responses) (14).

Dose intensity of gemcitabine in preclinical models was associated with efficacy. Although a clear dose-response relation cannot be made in the clinical setting due to heterogeneity in regimens, doses and patients, doses of gemcitabine as high as 2,200 mg/m² biweekly are known to be well tolerated, even in combination with capecitabine (15). The biweekly gemcitabine regimen has been an acceptable option in various other solid tumors, with good efficacy and even better convenience for patients (16-18). Similarly, the intermittent weekly capecitabine schedule has been found to be safe, well-tolerated and convenient, without compromising efficacy from the so far published data (15, 18).

In the present limited population experience, biweekly (every two weeks) schedule of gemcitabine delivery at 2000 mg/m² with capecitabine at a flat dose of 1000-1500 mg PO BID for 7 days followed by 7 days off seemed to promise the greatest potential for dose intensification with least toxicity. Given the nature of toxicities observed on this schedule as well as the history of previous chemotherapy regimens in these patients, this regimen provided a good platform to administer pegylated

filgrastim if indicated. This schedule is further supported by the study performed by Scheithauer *et al.* (15). However, it must be borne in mind that this study was constituted of chemo-naïve patients and haematological toxicity can be different. The present regimen needs to be explored, especially in KRAS mutant colon cancer patients and in those heavily pre-treated patients who for some reason haven't got the option of a clinical trial but are still fit enough to receive more treatment based on old drugs with modest activity, aiming for a longer disease control and better quality of life.

Conclusion

Evidence of disease control using the safe and well-tolerated combination of gemcitabine and capecitabine is demonstrated, which might allow oncologist to consider this option in selected CRC patients at advanced stages. Of course, high quality evidence can be only produced by properly designed prospective randomized studies.

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