Gemcitabine and Capecitabine as Third- or Later-line Therapy for Refractory Advanced Colorectal Cancer: A Retrospective Study

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Abstract. *Aim: To evaluate gemcitabine plus capecitabine as third-line or later-line therapy in patients with refractory advanced colorectal cancer (CRC) who maintain a good performance status (PS). Patients and Methods: We retrospectively evaluated patients who had failed at least two lines of therapy or had contraindication to standard therapy and received gemcitabine (1,000 mg/m^2, d1 biweekly) plus capecitabine (1,700 mg/m^2/day, d1-7 every two weeks) in a compassionate use program. Results: Thirty-nine patients were enrolled. The majority (85%) had ECOG PS 1. Gemcitabine plus capecitabine was administered as third- and fourth-line in 49% and 23% of patients, respectively; and as fifth-line or later-line in 28%. A clinical benefit of 21% was found. The median progression-free survival and overall survival were 3.0 and 7.3 months, respectively. Toxicity was mild to moderate, with no reported grade 4 toxicities. Conclusion: Gemcitabine plus capecitabine was safe and well-tolerated. While the efficacy of this regimen was modest in terms of response, the survival data were acceptable and consistent with previous publications on this setting.*

Colorectal cancer (CRC) is one of the most common causes of cancer mortality worldwide (1) and the second leading cause of cancer-related death in Europe (2). The combination of 5-fluorouracil (5-FU) and leucovorin (LV) with oxaliplatin and irinotecan has been the standard-of-care for advanced or metastatic CRC (3, 4). More recently, the addition of biological-targeted agents such as bevacizumab, cetuximab or panitumumab, to standard chemotherapy has resulted in improved outcomes in selected patients (5-9), although unresectable advanced CRC eventually becomes refractory to the available treatments. Despite progression on standard therapy, many patients maintain an excellent performance status, and third, fourth, or even later lines of therapy are generally offered to these patients. Nevertheless, there is currently no standard therapy for patients with refractory advanced CRC who are still in good condition, and offering this subgroup of patients a further line of therapy remains a challenge clinicians are faced with.

Gemcitabine, a nucleoside analog of deoxycytidine, exerts its antitumor activity through the inhibition of ribonucleotide reductase, the key enzyme responsible for the formation of deoxynucleotides required for DNA synthesis and repair. Although gemcitabine as a single-agent has demonstrated minimal activity in metastatic CRC (10, 11), clinical outcomes notably improve when gemcitabine is used in combination regimens in this setting. Pre-clinical studies have revealed that gemcitabine potentiates the antitumor activity of 5-FU (12). Capecitabine, an orally administered prodrug of 5-FU (13), is a tumor-selective fluoropyrimidine which has shown oven similar efficacy to bolus 5-FU with additional benefits in terms of safety and convenience (14-16). Phase I studies suggested that gemcitabine acts synergistically with fluoropyrimidines to enhance binding of

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thymidylate synthase and increase inhibition of DNA synthesis (17, 18), providing the basis for subsequent phase II studies exploring this combination in advanced CRC. However, the experience with gemcitabine plus fluoropyrimidines for advanced CRC refractory to currently available standard therapy is limited. The few phase II studies evaluating gemcitabine plus 5-FU as third-line therapy in advanced CRC (19-21) found stable disease in 31-70.5% of patients, median time-to-progression (TTP) was one to four months and median overall survival (OS) was nine to 11.3 months. The only phase II study conducted to date to assess the combination of gemcitabine plus capecitabine reported a TTP of four months and an OS of nine months, and some degree of activity was found (19). In view of these encouraging findings, the combination of gemcitabine with fluoropyrimidines may be a feasible and active alternative for patients with advanced CRC who have failed standard therapy and have limited options. However, the heterogeneity of patients, regimens and doses tested makes it difficult to draw firm conclusions concerning the efficacy of this regimen in heavily-treated patients with CRC.

On the basis of these promising findings, and considering the lack of standard therapy for refractory advanced CRC, we conducted a retrospective study to evaluate a modified schedule from the study of Fernández *et al*. (19), based on biweekly gemcitabine plus intermittent weekly capecitabine for compassionate use in patients with advanced CRC who had previously failed at least two lines of therapy.

Patients and Methods

Study design. This was a multicenter, retrospective, observational study aiming to evaluate the combination of gemcitabine plus capecitabine, administered as third-, fourth- or later lines of therapy for compassionate use in patients with advanced CRC. The study was conducted in seven Galician hospitals belonging to the Grupo Gallego de Investigaciones Oncológicas (GGIO) in which compassionate use of this combination had been previously approved. The study was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines and their amendments. Approval of the protocol was obtained from the Ethics Committee of Galicia (2010/507). Written informed consent was obtained from patients to retrospectively collect data from medical charts.

The primary study endpoint was the overall response rate (ORR) according to the Response Evaluation Criteria in Solid Tumors (RECIST) (22); secondary endpoints were progression-free survival (PFS), OS, and safety.

Patient population. We included all consecutive patients with advanced CRC patients (aged ≥18 years) who had failed or had contraindications to standard therapy and who were subsequently treated with gemcitabine plus capecitabine as third-line or later therapy in a compassionate use program under routine clinical practice conditions. There were not limitations to the number of prior received therapies. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, adequate renal, hepatic and bone marrow function and measurable disease by RECIST criteria. Information on Epidermal growth factor receptor (EGFR) and Kirsten rat sarcoma viral oncogene homolog (KRAS) status was not required.

Treatment. Compassionate treatment consisted of gemcitabine at 1,000 mg/m^2 as *i.v.* infusion on day 1 biweekly and oral capecitabine at 1,250 mg/m^2 twice daily on days 1-7 every two weeks. Treatment was continued until disease progression, unacceptable toxicity or death, whichever came first. The doses of gemcitabine and capecitabine could be either reduced or withheld based upon the degree of toxicity experienced by patients.

Pre-treatment and follow-up evaluation. The data were collected from patients' hospital records from the last visit before the initiation of treatment until death or loss to follow-up. Routine pre-treatment evaluation included a complete medical history, physical examination, blood analysis (hematology and biochemistry), ECOG performance status, imaging studies including chest X-ray, computed tomography or other examinations as needed. Tumor response assessment was routinely performed at weeks 12 and 24 according to the RECIST criteria version 1.1 (22). Patients were followed-up until disease progression or death (or last follow-up). Prior to each treatment cycle, physical examination and a complete blood cell count were performed and toxicity was assessed.

Statistical analysis. The primary objective of the study, ORR, was calculated as the sum of patients reaching a complete response and partial response as the best response achieved among the tumor evaluations of the study (at weeks 12 and 24). PFS was calculated as the time elapsed from the beginning of treatment until documented progression or death from any cause. OS was considered the time from the beginning of treatment to death. The probability of PFS and OS were estimated using the Kaplan Meier method. Patients were censored at the date of last available follow-up if still alive at the time of the analysis.

In order to assess toxicity per patient, the maximum grade for each of toxicity recorded during the cycles of treatment was considered for evaluation. Toxicities were graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) (version 3.0) (23).

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Patients' characteristics. Between June 2009 and July 2011, a total of 45 patients with refractory advanced CRC started therapy with gemcitabine plus capecitabine on a compassionate use basis. Four patients who had ECOG performance status >1 and two patients undergoing only one previous line of treatment were not evaluated. A total of 39 evaluable patients were analyzed. The median time (range) interval since first diagnosis to initiation of treatment was 2.4 (1.7-3.1) years. Patients' demographics, disease characteristics and prior treatment are detailed in Table I. The median age of patients was 66 (range 37-78) years and 69% were male. The majority of patients (85%) had ECOG

Table I. *Patients' demographic and clinical characteristics (n=39).*

Characteristic	Value
Median age (range), years	66 (37-78)
Missing data	1
Gender, n (%)	
Male	27 (69)
Female	12 (31)
ECOG performance status, n (%)	
0	5 (13)
1	33 (85)
Missing data	1 (2)
Primary tumor location, n (%)	
Colon	28 (72)
Rectum	6 (23)
Colon and rectum	3 (3)
Missing data	1 (2)
Number of metastatic sites, n (%)	
1	5 (13)
2	19 (49)
>2	10 (26)
Missing data	5 (13)
Metastatic sites, n (%)[a]	
Liver	32 (82)
Lung	25 (64)
Lymph nodes	10 (26)
Primary location	2 (5)
Previous surgical resection, n (%)	34 (87)
Missing data	1
Previous adjuvant treatment, n (%)[b]	
Chemotheraphy	12 (31)
Radiotherapy	6 (15)
No. of lines of prior therapy for advanced disease, n (%)	
2	19 (49)
3	9 (23)
≥4	11 (28)[c]

ECOG: Eastern Cooperative Oncology Group. Percentages may not add up to 100% due to the rounding. [a]Patients could have more than one metastasic site. [b]Missing data: n=4 for chemotherapy and n=6 for radiotherapy. [c]Seven patients (17.9%) had received four previous lines of therapy. Three patients and one patient had been previously treated with five and six lines of therapy, respectively.

Table II. *Previous anti-angiogenic and anti-epidermal growth factor receptor-based therapies for advanced disease.*

Previous therapies	N (%)[a]
First-line (n=39)	
FOLFIRI/bevacizumab	9 (23)
FOLFOX/bevacizumab	5 (13)
Capecitabine/bevacizumab	2 (5)
FOLFOX/cetuximab	2 (5)
FOLFIRI/cetuximab	1 (3)
XELOX/bevacizumab	1 (3)
Second-line (n=39)	
FOLFIRI/bevacizumab	9 (23)
FOLFIRI/cetuximab	5 (13)
Capecitabine/bevacizumab	2 (5)
Bevacizumab	1 (3)
Irinotecan/cetuximab	1 (3)
Tegafur/bevacizumab	1 (3)
Third-line (n=20)	
Irinotecan/cetuximab	5 (25)
FOLFIRI/bevacizumab	2 (10)
FOLFIRI/cetuximab	2 (10)
FOLFOX/bevacizumab	1 (3)
FOLFOX/cetuximab	1 (3)
Forth-line (n=11)	
FOLFOX/bevacizumab	2 (18)
Irinotecan/cetuximab	2 (18)
Bevacizumab	1 (9)
Capecitabine/bevacizumab	1 (9)
FOLFOX/cetuximab	1 (9)
Fifth-line (n=4)	
Irinotecan/cetuximab	2 (50)
FOLFOX/bevacizumab	1 (25)
Panitumumab	1 (25)

FOLFIRI: 5-Fluorouracil, leucovorin and irinotecan; FOLFOX: 5-fluorouracil, leucovorin and oxaliplatin; FUFA: fluorouracil/folinic acid. [a]Percentages were calculated of the total patients who received each line of therapy.

performance status of 1. In nearly three-quarters of patients, the primary tumor was located in the colon. Nearly half of the population had two metastatic sites (49%), and metastases were mostly located in the liver (82%) or lung (64%). Thirty-four (87%) patients had undergone resection of the primary tumor. Prior adjuvant chemotherapy was received by 30.8% of patients.

Previous therapy for advanced disease. Patients had received a median of three (range 2-4) lines of therapy prior to the use of gemcitabine and capecitabine. All patients had undergone at least two lines of treatment. All but five patients had received previous lines of therapy with targeted agents bevacizumab, cetuximab or panitumumab. Previous use of chemotherapy with antiangiogenic- or anti-EGFR-based therapy for advanced disease is detailed in Table II. Bevacizumab plus chemotherapy was the most frequent first-line treatment administered (36%), mainly combined with fluorouracil, leucovorin and irinotecan (FOLFIRI) (23%) or fluorouracil, leucovorin and oxaliplatin (FOLFOX) (13%), followed by a FOLFOX regimen (33%). Bevacizumab plus chemotherapy was also the most commonly used second-line treatment (31%), followed by cetuximab plus chemotherapy (15%). One patient (3%) was treated using bevacizumab alone as second-line therapy. One-quarter of patients had received cetuximab plus irinotecan as a third-line option. Among patients who had received a forth-line therapy, bevacizumab-based therapy and cetuximab plus chemotherapy regimens had been used in 27% of patients

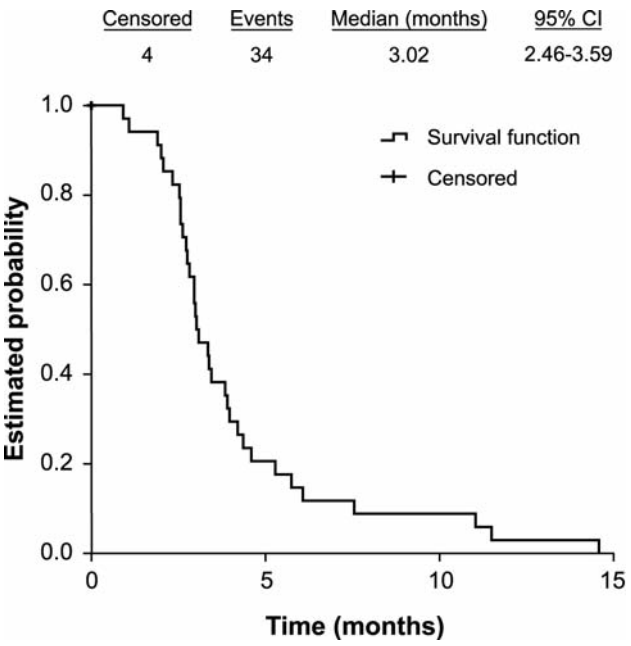

Figure 1. *Kaplan-Meier curve for progression-free survival in patients treated with gemcitabine and capecitabine combination as third-line or later-line therapy (n=38). 95% CI: 95% Confidence Interval.*

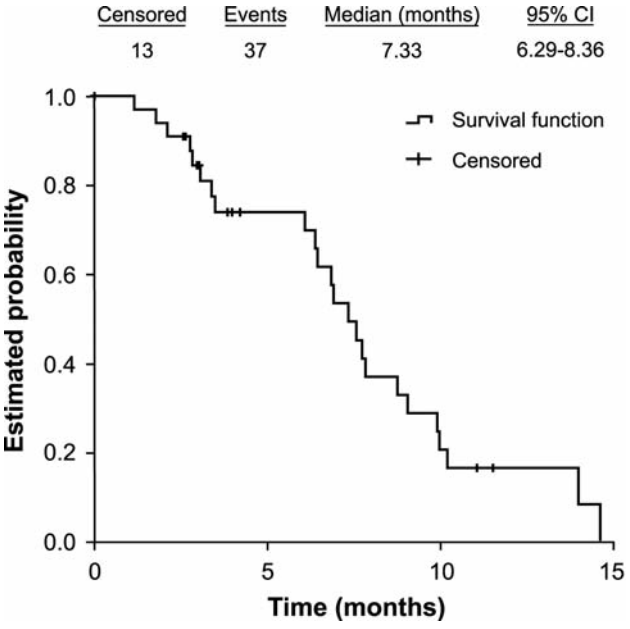

Figure 2. *Kaplan-Meier curve for overall survival in patients treated with gemcitabine and capecitabine combination as third-line or later-line therapy (n=37). 95% CI: 95% Confidence Interval.*

each respectively. Only one patient received panitumumab as a sixth-line treatment.

Treatment characteristics and modifications. The combination of gemcitabine and capecitabine was administered as third- or fourth-line in 19 (49%) and nine (23%) patients, respectively; and as fifth-line or later-line in 11 (28%) patients.

Patients received a median (range) of six (3-8) cycles of study treatment during a mean duration of 3.3±2.4 months. Seventeen (49%) patients did not require any treatment delay or dose reduction. Eighteen (51%) patients experienced at least one treatment modification. Seven (18%) patients required a dose reduction or treatment delay due to hematological toxicities. Thrombocytopenia and neutropenia was the reason for treatment delay or dose reduction in two patients each respectively, and in one patient a modification in the treatment schedule was needed due to the occurrence of both thrombocytopenia and neutropenia. Hepatic toxicity and hyperbilirubinemia were the reasons for treatment modification in two patients each, respectively.

Four patients (10%) continued treatment at the time of the analysis. The majority of patients (91%) had discontinued the treatment due to progressive disease. Toxicity was the cause of discontinuing therapy in four (9%) patients and worsening of clinical status led to treatment withdrawal in 2 (6%) patients.

Efficacy. Tumor response evaluation was not available in five patients at the time of the analysis. The ORR was 3% (1/34) [95% confidence interval (CI)=0.2-17.0] (one partial response). The clinical benefit rate (defined as the sum of patients achieving a complete response, partial response or stable disease) was 21% (7/34) (95% CI=9.4-38.4) (one partial response, six stable disease). Twenty-seven (79%) patients experienced disease progression during treatment. Thirty-eight and 37 patients were analyzed for PFS and OS respectively. The median duration of follow-up was 3.9 (2.6-8.0) months. The median PFS was 3.0 (95% CI= 2.5-3.6) months (Figure 1) and the median OS was 7.3 (95% CI=6.3-8.4) months (Figure 2). A one-year survival rate of 16% (95% CI=1.7-31.1%) was found. Twenty-four patients (61%) had died by the time of this analysis. Progression of the disease was the cause of death in all patients.

Safety. All patients enrolled in the study were considered evaluable for safety analyses (n=39). Toxicity was generally mild and manageable. Thirty-two (82%) patients experienced at least one toxicity during the study. No grade 4 toxicities were reported. The incidence of non-hematological and hematological toxicities is summarized in Table III. Hematological toxicities were infrequent and mild. The only grade 3 hematological toxicity was neutropenia in two patients. Six (15%) patients experienced non-hematological

Table III. *Treatment toxicity (n=39).*

Toxicity	NCI-CTC grade	
	Grade 1/2[a] N (%)	Grade 3[b] N (%)
Hematological		
Anemia	6 (15)	4 (10)
Thrombocytopenia	6 (15)	0 (0)
Neutropenia	1 (3)	2 (5)
Non-hematological		
Diarrhea	11 (28)	1 (3)
Mucositis	8 (20)	0 (0)
Nausea-vomiting	8 (20)	0 (0)
Asthenia	6 (15)	1 (3)
Constipation	3 (15)	0 (0)
Palmar-plantar erythrodysesthesia	1 (3)	2 (5)
Dyspnea	1 (3)	1 (3)
Fever	2 (5)	0 (0)
Hiperbilirubinemia	0 (0)	1 (3)

[a]Most common grade 1 or 2 toxicities detected in >5% of patients. [b]All grade 3 toxicities are recorded. No grade 4 toxicities were detected.

grade 3 toxicities, with palmar-plantar erythrodysesthesia as the most common toxicity (5%). The most frequent grade 1 or 2 non-hematological toxicities were diarrhea (28%), mucositis (20%), and nausea/vomiting (20%). None of the patients died as a result of treatment toxicity.

Discussion

The results of this study showed a limited response rate for the combination of gemcitabine and capecitabine in patients with refractory CRC, while the PFS and OS were acceptable in our population. This regimen was demonstrated to be safe and well-tolerated.

In our series, nearly all patients had received bevacizumab- or cetuximab-containing regimens in previous lines of therapy. Half of patients had received gemcitabine plus capecitabine as third-line therapy, with bevacizumab plus FOLFIRI being the main regimen used at the second-line setting. Bevacizumab as second-line therapy has been shown to extend OS in metastatic CRC (24, 25). However, at the time we initiated this study, limited to no efficacy had been reported with bevacizumab in the third- or later-line therapy (6, 25, 26). Although additional studies have found a modest activity with bevazicumab plus FOLFIRI or FOLFOX in third-line or beyond (27, 28), the role of this targeted agent in refractory CRC remains to be established (26, 27, 29, 30). On the other hand, cetuximab, has been shown to significantly improve the outcome of metastatic CRC compared to best supportive care-alone in the third-line setting (31). In our series, cetuximab-based combinations have been the most frequent third-line regimens used preceding gemcitabine plus capecitabine.

Our results do not confirm the efficacy figures previously reported with gemcitabine plus fluoropyrimidines in previous phase I/II and phase II studies (19-21) reviewed by Merl *et al*. (25), wherein the median OS time was 9 to 11.3 months, and the ORR ranged from 30% to 38.3%. In particular, our findings do not support the only exploratory study conducted so far to assess gemcitabine plus capecitabine in heavily-treated metastatic CRC (19), in which a median OS of nine months was reported. However, there are some differences concerning previous treatments that could explain the apparently worse outcome of our series compared with these studies. A possible explanation for our series failing to reach a better outcome may be that the majority of patients of our series had previously gone through the most active standard therapies for CRC before being submitted to the third- or fourth-line, whereas patients included in the previous studies had generally received chemotherapy without targeted agents in prior lines of therapy.

Furthermore, the heterogeneity in patients, schedules and doses evaluated in the few available studies of gemcitabine plus fluoropyrimidines are insufficient to reach firm conclusions about the efficacy of this approach in refractory CRC. Likewise, most studies were published as meeting abstracts, where information was not complete. A recent retrospective study assessing biweekly gemcitabine plus capecitabine as fourth-line and later-line therapy found a modest activity for this combination (32). Contrary to previous phase II studies assessing gemcitabine and 5-FU or capecitabine, all patients included in this study had previously been treated with biological agents. The disease control rate also appears to be superior in this study as compared with our series, although survival data were not reported and the toxicity profiles were not detailed. One possible explanation for the differences regarding the response rates could be the higher doses of gemcitabine used as compared with our schedule.

While a limited benefit in tumor response was seen in our study, some efficacy in terms of survival was found. This treatment seems to offer a modest median OS which compares favorably with the survival data seen in previous studies with other therapeutic alternatives for heavily-treated CRC, such as mitomycin-based based regimens (33-35). Additionally, compared to historical data, our regimen appears to allow for a superior median OS than other third-line data with best supportive care, where a median survival of about five months was found (9, 31). As a descriptive comparison only, our data on PFS and OS do not seem to be worse than the survival data recently reported from a phase II study with tivozanib and everolimus for refractory metastatic CRC (PFS: 3 months; OS: 5.6 months) (36) and those obtained in the CORRECT study with the new multitargeted tyrosine kinase inhibitor

regorafenib in patients with metastatic CRC who failed all approved standard therapies including biological agents (PFS: 1.9 months; OS: 6.4 months) (37).

New agents or combinations have shown promising efficacy for heavily-treated advanced or metastatic CRC in various phase II studies such as TIROX (S-1 plus irinotecan and oxaliplatin) (38), bevacizumab plus everolimus (39), perifosine plus capecitabine (40), and more recently, the novel oral nucleoside antitumour agent TAS-102 (41). However, further clinical studies are required to demonstrate the benefit of these regimens. Clinicians are facing with a shortage of novel promising agents and treatment approaches to manage refractory metastatic CRC. Indeed, it has been several years since the last new agents, bevacizumab, cetuximab and panitumumab, were introduced into the therapeutic armamentarium for metastatic CRC. Regorafenib is the first small-molecule, multikinase inhibitor with proven activity in metastatic CRC and this agent has recently obtained US Food and Drug Administration approval for metastatic CRC in the salvage setting. However, there is no biomarker to identify which patient subgroups are most likely to benefit from regorafenib and whether this agent will be valuable in combination with chemotherapy is currently unknown.

Toxicity is a particularly important concern in patients with advanced CRC who have undergone multiple lines of therapy. The exploratory study by Fernández *et al*. showed an excellent tolerability for gemcitabine at 900 mg/m^2 on day 1 administered biweekly with capecitabine 2,500 mg/m^2 *bid* on days 1-7 every two weeks (19). Accordingly, we found that the modified gemcitabine-plus-capecitabine regimen used in our series was safe and well-tolerated. Toxicity was generally mild and manageable. Interestingly, no grade 4 toxicities were detected and none of the patients died due to treatment toxicities. Previous studies with gemcitabine plus fluoropyrimidines reported neutropenia, thrombocytopenia and mucositis as the major grade 3-4 toxicities. The most common grade 3-4 toxicities found in our series were neutropenia and hand-foot syndrome. No grade 3-4 thrombocytopenia was detected, and conversely to Fernández *et al*., we did not find grade 4 mucositis. Consistent with previous studies with gemcitabine plus 5-FU or capecitabine, only ≤8% of patients experienced neutropenia. Dose reduction or treatment delay due to hematological toxicity was only required in eight (18%) patients and only four (9%) discontinued therapy because of toxicity.

The main limitations of our study arise from the small population analyzed and its retrospective nature. Moreover, this series seem to be heterogeneous in relation to the number of preceding therapy lines. However, it is important to emphasize that this could be considered a consistent group of patients considering that all of them had exhausted the main current therapeutic options for their advanced disease, regardless of the sequence, and were still fit enough to receive further treatment. Other potential limitation could be the choice of the principal variable. Considering that responses are generally rare in refractory CRC and given that stabilization of disease is clinically meaningful in this setting, we should have calculated the sample size of the study on the basis of clinical benefit rate, instead of considering ORR.

In summary, while the results from our series are modest in terms of response rate, the survival data are acceptable and consistent with those obtained with other approaches assessed for refractory advanced CRC. However, although some of the regimens tested have demonstrated a certain degree of efficacy in refractory advanced or metastatic CRC, there is presently no standard therapy in this setting. Despite the obvious limitations arising from this retrospective study, our findings, although modest, might offer an addition to the limited available experience with gemcitabine plus capecitabine for refractory CRC. Additionally, further investigation of this combination with higher gemcitabine doses may be considered aiming for an increased efficacy. This would be particularly important in less heavily-treated patients without other options, or in patients carrying KRAS mutations, who are not suitable for clinical trials with new agents or combinations and who are still fit enough to receive further treatment.

In conclusion, biweekly gemcitabine plus intermittent weekly capecitabine was a safe and well-tolerated regimen with modest efficacy in patients with advanced CRC who have progressed after all standard therapies, including targeted agents. Larger randomized trials will be needed to assess the possible role of this regimen in the management of refractory CRC.

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