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ORIGINAL ARTICLE

Capecitabine plus temozolomide (CapTem): An alternative regimen to regorafenib as third-line setting in metastatic colorectal cancer?

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Summary

Purpose: *The optimal treatment regimens after second line chemotherapy in metastatic colorectal cancer (mCRC) remains unclear. This study aimed to compare the real-life data of regorafenib versus capecitabine plus temozolomide (CapTem) regimen as third-line setting in mCRC.*

Methods: *Between January 2013 and March 2018, data of 358 mCRC patients were retrospectively evaluated. Forty-two mCRC patients who received regorafenib (n:27) or CapTem (n:15) as third-line setting were included.*

Results: *Median follow-up was 6 months (range: 2.2-29.7). No complete remission was achieved. Disease control rate was 22% and 20% for the regorafenib and CapTem arms, respectively. There was no statistically significant difference for either median overall survival (OS) or progression-free survival (PFS) between the two groups. Median OS was 7 months in the regorafenib group and 6.5 months in the CapTem group (hazard ratio [HR] for death, 0.60; 95% confidence interval [CI] 0.28-1.27; p=0.18), and median PFS was 3.3 months for the patients in the regorafenib group and 3.2 months for those in the CapTem group (HR for disease progression or death, 0.68; 95% CI 0.34-1.33; p= 0.25).*

Conclusion: *The present study showed that CapTem regimen and regorafenib as third-line setting had similar activity in mCRC. We consider that CapTem regimen might be an alternative treatment option to regorafenib after two lines of chemotherapy in mCRC. However, prospective randomized trials with large number of patients are needed in this issue.*

Key words: *metastatic colorectal cancer, regorafenib, capecitabine plus temozolomide, beyond second-line therapy*

Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer-related deaths worldwide [1-3]. Nearly 20% of CRC patients have metastasis at diagnosis [4]. The treatment is palliative in the majority of these patients and the goal of treatment is to increase the quality of life and prolong overall survival (OS) [5].

Median OS has reached 3 years with addition of biological agents such as anti-VEGF (Vascular Endothelial Growth Factor) agents (i.e. bevacizumab, ziv-aflibercept) and anti-EGFR (Epidermal Growth Factor Receptor) agents (i.e. cetuximab, panitumumab) for left-sided ras-wild type metastatic colorectal cancer (mCRC) to 5FU-based chemotherapy, but the 5-year survival rate is less than 20% in mCRC [6-7]. However, the optimal chemotherapy regimen is unclear for the patients with mCRC beyond second-line therapy. National Comprehensive Cancer Network (NCCN) recommends regorafenib, trifluridine-tipiracil (TAS-102), nivolumab and pembrolizumab [for those with microsatellite instability (MSI-H)] for these patients [8].

Regorafenib is an orally active multikinase inhibitor (i.e. VEGF, FGF, PDGF, BRAF, KIT, RET

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inhibitor) [9]. In phase 3 trials, regorafenib was shown to have efficacy in refractory mCRC [10-11].

O6-methylguanine DNA methyltransferase (MGMT) is a DNA repair enzyme and its transcription is regulated by epigenetic mechanisms [12]. MGMT is responsible for DNA repair following administration of alkylating agents. MGMT can be silenced by the promoter methylation of the gene. Promoter methylation leads to increased chemotherapy sensitivity by inhibiting DNA damage repair. Temozolomide (TMZ) is an oral alkylating agent which shows its cytotoxic effect by DNA methylation. It has *in vitro* activity against many malignancies including colorectal cancer [13]. Low expression of MGMT is reported in 27-40% of mCRC patients [14]. Amutu et al reported disease control rate (DCR) 44% for MGMT-hypermethylated refractory mCRC patients [15]. In another retrospective study, ORR was 12% with a median progression-free survival (PFS) 1.8 months and median OS 8.4 months, respectively [16].

Fluoropyrimidines are accepted as standard first-line agents in CRC, and capecitabine is an oral fluoropyrimidine pro-drug [17]. Fine et al. reported a synergistic effect between TMZ and capecitabine (CapTem), and this combination regimen became one of the most common used regimens in some solid tumor types, such as metastatic neuroendocrine tumors [18,19]. In a recent phase 2 study which included 40 patients with KRAS wild-type refractory mCRC, median PFS and median OS were 1.9 and 7.1 months, respectively [20].

To our knowledge, our retrospective study is the first to compare regorafenib with CapTem regimen in refractory mCRC.

Methods

Patient characteristics

We screened retrospectively the file data of 358 mCRC patients between January 2013 and March 2018. Patients who were given regorafenib and CapTem regimen as third-line setting were enrolled.

Inclusion criteria

Patients aged ≥18 years, Eastern Cooperative Oncology Group performance score (ECOG-PS) ≤2, with histologically proven CRC and metastatic disease that could be measured according to the criteria of Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1), previously received fluoropyrimidine, oxaliplatin and irinotecan as first-line or second-line palliative therapy with adequate liver, bone marrow and renal functions. The patients who did not meet the inclusion criteria and those with brain metastases were excluded from the study.

The demographic and clinicopathological data of the patients were recorded. Toxicity analysis was not performed because the data about toxicity were inadequate.

Regorafenib was administered as 160 mg/day, 1-21 days, every 28 days. Dose adjustment was made according to tolerability during treatment (i.e. de-escalation to minimum 80 mg/day). In CapTem regimen, capecitabine was administered as 750 mg/m^2, bid, 1-14 days, every 21 days with temozolomide as 150-200 mg/m^2 day, 10-14 days, every 28 days.

Procedure

All patients underwent physical examination, hematological and biochemical evaluation every 2 weeks on the first cycle and then on the first day of each cycle. Tumor response was assessed by computerized tomography (CT) or positron emission tomography/computed tomography (PET/CT) every 12 weeks according to RECIST criteria (v1.1). According to RECIST criteria, complete response (CR) was defined disappearance of all target lesions and reduction in the short axis measurement of all pathologic lymph nodes to ≤10 mm; partial response (PR) was defined as ≥30% decrease in tumor size; progressive disease (PD) was defined as ≥20% increase in tumor size or appearance of new lesion(s); stable disease (SD) was neither PR nor PD. Disease control rate (DCR) was defined as the sum of complete response, partial response and stable disease rates.

Factors assessed in univariate and multivariate analysis

Based on previous studies, 12 variables were selected, which could effect the overall survival [21,22] The variables were divided into two categories: age (<65 or ≥65 years), sex (male or female), ECOG- performance status (0-1 or 2), tumor localization (right or left, rectum or colon), KRAS mutation status (mutant or wild), number of metastatic sites (1 or ≥2), liver, lung and peritoneal metastasis (present or absent), duration of metastatic disease (<18 months or ≥18 months) and treatment choice (Regorafenib and CapTem).

Statistics

Statistical analyses were performed by using Statistical Package for the Social Sciences Version 22.0 for Windows (SPSS Inc., Chicago, IL, USA). Patient characteristics and response rates were compared by Pearson chi-square test and Fisher's exact test. Kaplan-Meier method was used for survival analysis and survival outcomes were analysed by Log-rank test. The Cox proportional hazards model was applied for multivariate analysis. P value less than 0.05 was considered as statistically significant.

The duration from starting third-line treatment (i.e. regorafenib or CapTem regimen) until progression was defined as PFS, whereas until death or date of last known alive was defined as OS.

Results

Forty-two patients with mCRC were included in the study. Median age was 57 years (range: 31-74). There were 27 patients (Male/Female=2.3) in the

Table 1. Baseline characteristics

Characteristics	*Regorafenib* (n=27) n (%)	*CapTem* (n=15) n (%)	*p value*
Age (years)			0.1
Median (range)	57 (35-74)	56 (31-71)	
<65	23 (85)	10 (67)	
≥65	4 (15)	5 (33)	
Sex			0.8
Female	8 (30)	5 (33)	
Male	19 (70)	10 (67)	
ECOG performance status			0.4
0	5 (19)	2 (13)	
1	19 (70)	11 (73)	
2	3 (11)	2 (13)	
BMI (kg/m^2)			0.5
Median (range)	23.8 (19-39)	24 (20-36)	
<25	16 (64)	9 (60)	
≥25	9 (36)	6 (40)	
Main site of disease			0.1
Rectum	10 (37)	9 (60)	
Colon	17 (63)	6 (40)	
Tumor localization			0.8
Left	23 (85)	13 (87)	
Right	4 (15)	2 (13)	
Histology			0.2
Adenocarcinoma	25 (93)	12 (80)	
Mucinous carcinoma	2 (7)	3 (20)	
KRAS			0.8
Mutant	12 (44)	7 (46)	
Wild	15 (56)	8 (54)	
Number of metastatic sites			0.6
Single	4 (15)	3 (20)	
Multiple	23 (85%)	12 (80%)	
Metastatic regions			
Liver/Lung/Periton/Bone	24/14/9/1	14/12/1/3	
Time from diagnosis of metastatic disease (months)			0.4
Median (range), months	16.7 (6-46.8)	20.7 (6.6-55)	
<18	14 (52)	6 (40)	
≥18	13 (48)	9 (60)	
Previous drug treatment			0.5
Fluoropyrimidine	27 (100)	15 (100)	
Oxaliplatin	27 (100)	15 (100)	
Irinotecan	27 (100)	15 (100)	
Anti-VEGF treatment	25 (93)	15 (100)	
Anti-EGFR treatment	12 (44)	8 (53)	
Any (VEGF or EFGR)	25 (93)	15 (100)	
Previous surgery			0.9
Primary tumor resection	12 (45)	7 (47)	
Primary + Metastasectomy	6 (22)	3 (20)	
No surgery	9 (33)	5 (33)	

CapTem:capecitabine plus temozolomide, ECOG:eastern cooperative oncology group, BMI:body mass index, VEGF:vascular endothelial growth factor, EGFR:epidermal growth factor receptor

regorafenib group and 15 patients (M/F= 2: 1) in the CapTem group. The clinicopathological characteristics of the patients are summarized in Table 1.

Median follow-up was 6 months (range: 2.2-29.7) for all patients while it was 5.6 months for regorafenib group and 6.5 months for CapTem group in subgroup analysis. The patients in both groups had similar treatment duration and dose modification rates. Median treatment duration was 2.9 months in the regorafenib group and 2.3 months in CapTem group (p=0.1). Dose modification was performed in 64% of patients in the regorafenib group and 60% in the CapTem group. Initial dose was 160 mg/day in most of patients (73%) who received regorafenib. Twenty-five patients (93%) in the regorafenib group and 15 patients (100%) in CapTem group had previously received biological agents (Anti-VEGF and/or Anti-EGFR) with chemotherapy.

No patients achieved CR. PR rate was 7% in both groups and DCR was 22% and 20%, respectively. Response rates are summarized in Table 2. There was no statistically significant difference for either OS or PFS. Median OS was 7 months (95% CI 1-12.9) in the regorafenib group and 6.5 months (95% CI 1.9-11.1) in the CapTem group (hazard ratio [HR] for death, 0.60; 95% CI 0.28-1.27; p=0.18).

Table 2. Tumor response

Responses	*Regorafenib*	*CapTem*
	(n=27)	*(n=15)*
	n (%)	*n (%)*
CR	0	0
PR	2 (7)	1 (7)
SD	4 (15)	2 (13)
PD	21 (78)	12 (80)
Objective response rate	7%	7%
Disease control rate (CR+PR+SD)	22%	20%

CR:complete response, PR:partial response, SD:stable disease, PD:progressive disease

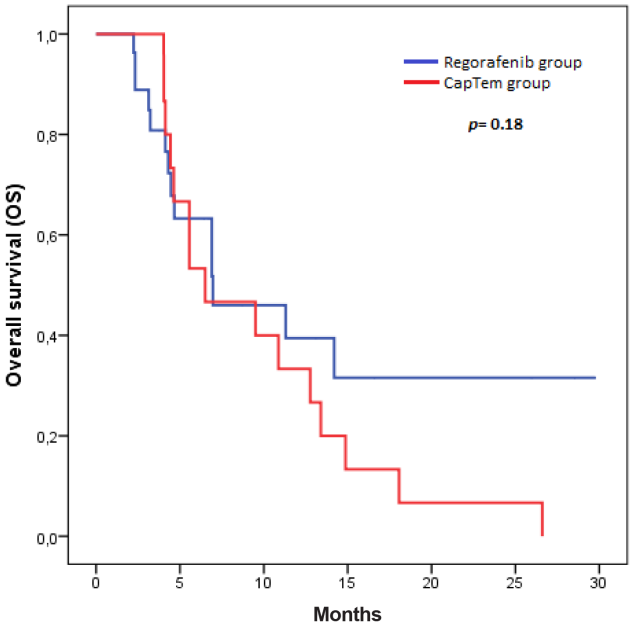

Figure 1. Kaplan-Meier curves for overall survival (CapTem: Capecitabine Plus Temozolomide).

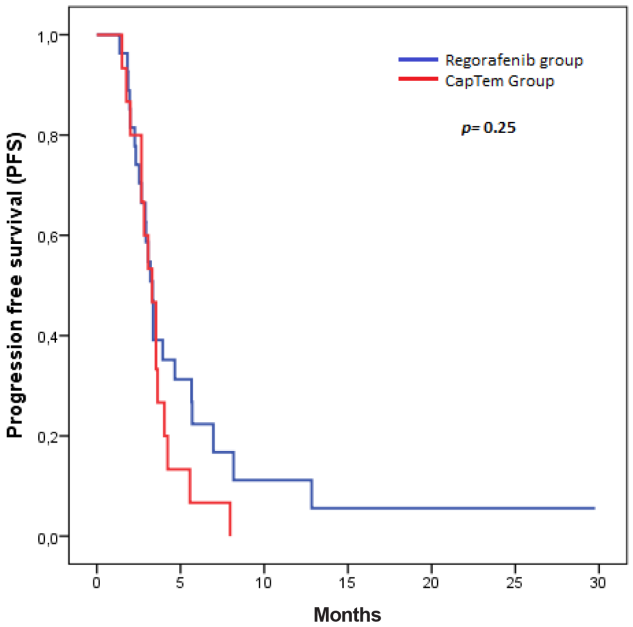

Figure 2. Kaplan-Meier curves for progression-free survival (CapTem: Capecitabine Plus Temozolomide).

Table 3. Multivariate analysis of potential prognostic factors associated with overall survival

Factors	*HR*	*95% CI*	*p value*
Treatment group			
Regorafenib	0.5	0.22-1.15	0.1
KRAS, mutant	1.2	0.45-3.18	0.7
Tumor localization, left	1.1	0.31-4.0	0.8
Time from diagnosis met. <18 months	2.1	0.84-5.34	0.1
Number of metastasis sites, single	0.4	0.13-1.63	0.2

HR: hazard ratio, 95% CI: 95% confidence interval

OS curves are shown in Figure 1. In addition, median PFS was 3.3 months (95% CI 2.9-3.7) for the patients in the regorafenib group and 3.2 months (95% CI 2.6-3.9) for those in the CapTem group (HR for disease progression or death, 0.68; 95% CI 0.34-1.33; p=0.25) (Figure 2).

None of the factors assessed in univariate and multivariate analysis had prognostic significance for PFS and OS. On the other hand, none of these factors could have been defined as a predictive factor. Multivariate analysis results for OS are summarized in Table 3.

Discussion

The patients with chemorefractory mCRC have poor prognosis and median OS is less than 1 year [10,11]. Optimal treatment options, especially after second line therapy, are limited in these patients. To best of our knowledge, our study is the first to compare regorafenib and CapTem regimen as third-line treatment after failure with standard fluoropyrimidine-based regimens in mCRC.

In our study, there was no survival difference between regorafenib and CapTem groups (7 *vs* 6.5 months, p=0.18). Regorafenib and TAS 102 compared to placebo beyond second-line therapy was shown have survival advantage in phase 3 trials [10,11,23]. In REBECCA study 656 patients were evaluated and their median OS was 5.6 months in the regorafenib group [21]. So, in our study, median OS in both groups was consistent with regorafenib trials. Single-agent temozolomide activity in mCRC has been evaluated in some trials and was reported to have greater efficacy with a median OS 6 months benefit in MGMT-methylated ones [16,24-26]. However, data is limited for third-line CapTem regimen for these patients in the literature. Qvortrup et al reported 7 months of survival advantage with CapTem regimen in mCRC [20]. In our study, we were not able to evaluate our patients for MGMT analysis since it was a retrospective study with a relatively small sample size. This was one of our limitations. However, median OS was 6.5 months in the CapTem group. We consider that our survival outcomes might have been better if we could select MGMT-methylated patients for CapTem regimen group. So, this point should be evaluated in a prospective study with larger sample size.

In our study, there was no statically significant difference for PFS (3.3 *vs* 3 months respectively, p=0.25). Median PFS with regorafenib was 1.9 months in CORRECT trial and 3.2 months in CONCUR trial, whereas it was 2 months with TAS-102 in RECOURSE trial in pretreated patients [10,11,23]. In our study, median PFS in CapTem group was longer than that reported in the literature. Qvortrup et al reported a PFS of 1.9 months with CapTem regimen [20]. It was around 2-2.5 months with single-agent temozolomide [24,26]. The radiological evaluation was done every 12 weeks in our study, while it was done every 8 weeks in other studies. This may be the reason why PFS with CapTem regimen in our study was longer than in other studies.

In our study, ORR (7%, all PR) and DCR (22 *vs* 20%) were similar in the two groups. In CORRECT and CONCUR trials, CR could not have been achieved with regorafenib and PR was 1 and 4%, respectively [10,11]. They had higher DCR (40 and 51%), probably related to higher disease stabilization rather than regression. We could not compare the tumor response rates of the CapTem regimen in the literature.

There have been conflicting outcomes for prognostic significance of any factors in the literature [21,22]. REBECCA trial is a large cohort in which survival outcomes of regorafenib in real-life setting were reported [21]. In this trial, ECOG PS, duration of delay in treatment iniation, initial regorafenib dose, number of metastatic sites, and presence of liver metastasis were defined as prognostic factors. On the other hand, Gotfrit et al failed to show any prognostic factor in this setting [22]. In our study, we did not find out any prognostic factor for PFS and OS, and we were not able to define any predictive factor for either regorafenib or CapTem regimen as well. We believe that prognostic and predictive markers should be evaluated in prospective randomized clinical trials in this area.

We are aware of the limitations in our study. First of all, it is a retrospective study with a relatively smaller sample size, especially for the CapTem arm. It might have contributed to the failure of better documentation of prognostic and predictive markers. Additionally, in this retrospective design, toxicity of both groups could not have been well documented. However, we know that toxicity rates and their management have great significance as well as efficacy of any therapeutics, especially in heavily pretreated metastatic cancer patients. If we had documented toxicity rates and dose adjustments according to the toxicity grades, we could have contributed more to the literature in terms of a *'less toxic, most effective'* treatment option as third-line treatment in mCRC. Finally, we could not have analyzed our patients for MGMT mutation status as we mentioned above. If we could have selected *'MGMT mutated'* subgroup for CapTem arm, we might have had better survival outcomes. However, besides these limitations, we believe that our study has clinical significance since it has real-life data in which two different arms (i.e. regorafenib &

CapTem regimen) were retrospectively compared for clinicopathological characteristics and survival outcomes. To our knowledge, there is no more data about this comparison in the literature.

Conclusions

In conclusion, to our knowledge, there is no more data about comparison of third-line regorafenib and CapTem regimen in mCRC in the literature. Currently, TAS-102 and immunotherapy (for MSI-H tumors) seem to be other options in this setting. However, it might be difficult to access these agents, especially in developing countries, and regorafenib and CapTem regimen seem to have similar efficacy in these patients. So, CapTem regimen might be another option besides regorafenib in these circumstances. However, we need further clinical trials to compare regorafenib and CapTem regimen 'head-to-head' for clinical outcomes.

Conflict of interests

The authors declare no conflict of interests.

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