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Research Article

Real World Study on Regorafenib for Metastatic Colorectal Cancer in the Beyond-Second-Line Setting in Macau

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Abstract

Objective: Approved treatments for metastatic colorectal cancer (mCRC) beyond the second-line included regorafenib. We intended to elucidate the proportion of patients with mCRC who failed to receive regorafenib and to identify baseline patient characteristics which might be predictive of ineligibility for regorafenib.

Methods: A retrospective chart review was performed for all the patients who experienced failure of standard 1st and 2nd-line treatment for mCRC in our hospital. Comparison was made between patients who had exposure to regorafenib and those who did not. Logistic regression was utilized to identify predictors for ineligibility of regorafenib.

Results: Among 70 enrolled patients, 39 failed to receive regorafenib. 22 were truly ineligible for regorafenib. The regorafenib group was superior to the non-regorafenib group regarding median overall survival (mOS) beyond-2nd line (8.0 versus 3.8 months, Hazard ratio 0.292) and survival from diagnosis of mCRC (34.9 versus 18.9 months, Hazard ratio 0.432). Presence of peritoneal metastases upon diagnosis of mCRC (Odds ratio 4.491) was found to be associated with ineligibility for regorafenib. **Conclusions:** 31.4% of the patients with mCRC were ineligible for regorafenib as salvage therapy upon failure of 2nd line treatment. Peritoneal metastasis was found to be associated with future ineligibility for regorafenib.

Keywords: Metastatic colorectal cancer; Treatment beyond second-line; Ineligibility for regorafenib

Abbreviations

mCRC: Metastatic Colorectal Cancer; CRC: Colorectal Cancer; VEGF: Vascular Endothelial Growth Factor; EGFR: Epithelial Growth Factor Receptor; mOS: Median Overall Survival; OS: Overall Survival; TTF: Time to Treatment Failure; ECOG PS: Eastern Cooperative Oncology Group Performance Status; CCI: Chalson Co-Morbidity Index; HR: Hazard Ratio; 95% CI: 95% Confidence Intervals; OR: Odds ratio.

Introduction

Standard 1st and 2nd-line treatment for metastatic colorectal cancer (mCRC) involves combinational or sequential use of fluoropyrimidines, oxaliplatin, irinotecan, along with target therapy targeting vascular endothelial growth factor (VEGF), as well as mono-antibodies (cetuximab and panitumumab) targeting epithelial growth factor receptor (EGFR) in patients who have KRAS wild-type tumors. Regulatory-approved choices of treatment in beyond 2nd-line setting for mCRC which does not have microsatellite instability included regorafenib and trifluridine/tipiracil [1].

Regorafenib is an oral multikinase inhibitor that blocks the activity of several protein kinases associated with angiogenesis, oncogenesis, and the tumor microenvironment [2]. The survival advantage of regorafenib over placebo for patients with mCRC who had progressed on standard therapies was demonstrated by two prospective randomized trials named CORRECT [3] and CONCUR [4]. Several large-scale post marketing trials aiming primarily at safety issues [5-8] and dozens of single-center studies [9,10] yielded survival outcomes of mCRC patients treated with regorafenib in real world setting comparable to those in precedent randomized trials. However, most of these studies were single-armed, with some among them attempting to investigate the survival-predictive value of imaging features like cavity within lung metastatic lesions elicited by regorafenib [11] or particular treatment emergent toxicity such as hand-foot-skin-reaction [7].

The purpose of our study is different. First, we sought to know, among all the mCRC patients who just experienced failure of both 1st and 2nd line treatment, the proportion of patients who were ineligible for further salvage treatment, namely regorafenib. Second, we want to identify features of mCRC patients which were predictive of future ineligibility for regorafenib in the beyond 2nd-line setting.

Colorectal cancer (CRC) has an annual incidence of 250 new cases and was the second leading cause of cancer death (99 cases) in Macau in 2015 [12]. Being the only government-managed hospital in such an enclosed community like Macau which provides all the

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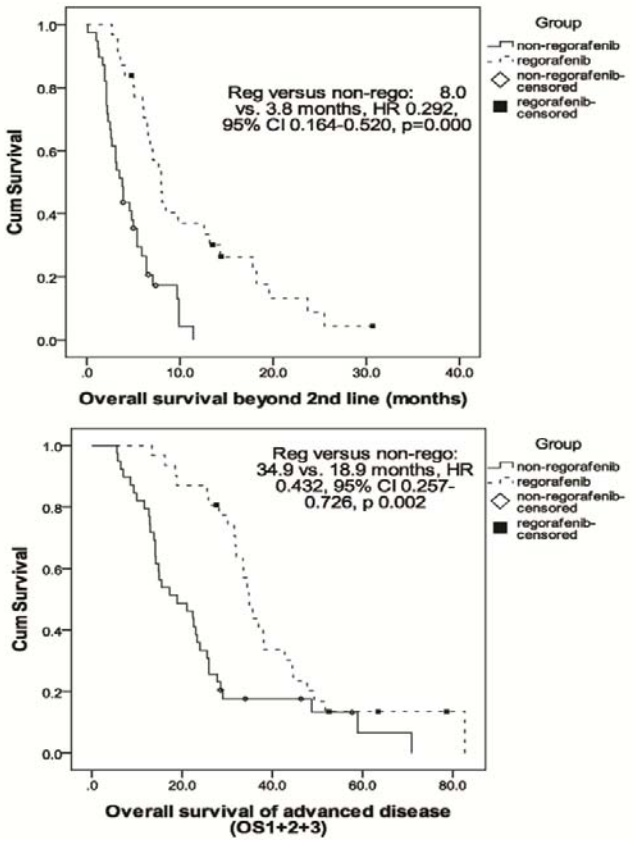

Figure 1: Overall survival (OS) of patients with exposure to regorafenib (n=31) in beyond 2nd-line setting relative to patients without (n=39): The regorafenib group was superior to the non-regorafenib group regarding both the OS calculated from the failure of 2nd line treatment (Figure 1a) and that calculated from the diagnosis of metastatic colorectal cancer (Figure 1b).

agents commonly used for mCRC except trifluridine/tipiracil and ramucirumab for each eligible mCRC patient at no cost, Centro Hospitalar Conde de São Januário constitutes an excellent scenario for real-world investigation of regorafenib in the beyond 2nd-line treatment of mCRC.

Materials and Methods

Data source and cohort selection

A retrospective chart review of medical records was performed for all the patients who received medical care in the department of medical oncology of Centro Hospitalar Conde de São Januário due to advanced colorectal cancer between January 1st 2014 and Oct 30th 2017.

The selection criteria of cases eligible for analysis regarding systemic therapy for mCRC beyond 2nd-line were as follows: The patient (a) had histopathologically confirmed colorectal adenocarcinoma; (b) developed advanced disease including metachronous irresectable local recurrence and/or distant metastases after precedent radical resection, or de novo synchronous irresectable metastases (including potentially resectable liver and/or lung metastases); (c) had ECOG PS 0-1 and adequate organ function for intensive systemic therapy upon the emerging of advanced diseases; (d) had already experienced combined treatment failure of standard 1st and 2nd-line chemotherapy for mCRC which comprised all the following agents, namely fluoropyrimidine (fluorouracil, capecitabine, Tegafur/gimeracil/oteracil), oxaliplatin, irinotecan, and cetuximab or panitumumab for K-RAS and N-RAS (codons 12, 13, 61, 117, 146) wild type tumor. Exposure to bevacizumab and/or aflibercept was not mandatory. Treatment failure was defined as disease progression during or within 3 months after discontinuation of treatment, or serious treatment emergent adverse events which prohibits any further re-challenge. Reintroduction of oxaliplatin which was discontinued longer than 6 months before disease recurrence/progression and re-challenge with irinotecan in combination with anti-EGFR antibody for anti-EGFR antibody naïve patient with irinotecan-resistant disease was regarded as part of the standard 1st and 2nd-line therapy.

Given that regorafenib was administered to the 1st mCRC case in our hospital on September 1st 2014 and the follow-up ended on October 30th 2017, only patients who experienced combined treatment failure of 1st and 2nd-line therapy as above-defined between August 1st 2014 and April 30th 2017 were selected for analysis.

Data collection

Those selected cases were separated into two groups according to whether they had exposure to regorafenib in the beyond 2nd-line treatment for mCRC or not. Patient characteristics listed in Table 1 were abstracted for all cases. To assess the prevalence of comorbid disease in our cohort, we used the Charlson comorbidity index (CCI) [13] assessed at the time of diagnosis of mCRC with the 6 points for mCRC excluded. Time to combined treatment failure of 1st plus 2nd line treatment (TTF_{1+2}) was calculated from the date of diagnosis of advanced disease (Day 1) to the date of treatment failure of all standard 1st and 2nd-line agents for mCRC (Day 2). Overall survival beyond 2nd-line (OS_{b2}) and overall survival of advanced disease (OS_{1+2+3}) were defined as the duration from Day2 and Day1 respectively till death from any cause or censoring on the last follow-up date. For comparison of overall survival relative to the results from precedent studies, median overall survival between the date of initiating regorafenib and the date of death or censoring (OS_{rego}) was also calculated for patients who took regorafenib. Progression-free survival was not evaluated due to heterogeneous radiologic assessment in clinical practice.

Statistical analysis

Continuous and categorical variables were presented as median (interquartile range) and number (proportion) of patients, respectively. Statistical tests were 2-sided with 5% significant level. Wilcoxon rank-sum tests were used to compare continuous variables while Chi square tests or Fisher's exact test were used for categorical variables. Time-to event endpoints such as TTF_{1+2}, OS_{b2}, OS_{rego} and OS_{1+2+3} were plotted by the Kaplan-Meier method. OS_{b2} and OS_{1+2+3} were compared between regorafenib group and non-regorafenib group by the log-rank test with hazard ratios (HR) and 95% confidence intervals (95% CI) computed using the Cox proportional hazards model. The impact upon OS_{b2} of co-variates besides exposure to regorafenib was analyzed using univariate cox regression. Binary logistic regression (method, forward: LR) was utilized to analyze the impact of possible predictors on the failure and ineligibility for receiving regorafenib in beyond 2nd-line setting.

Table 1: Patient characteristics till failure of 1st and 2nd line treatment.

		Regorafenib group (n=31)	Non-Regorafenib group (n=39)	P value (2-sided) [a, b]
Age of diagnosis of advanced CRC on Day1	median (Interquartile range)	60(52.3-62.9)	57(52.5-67.0)	0.986[a]
	<=65 years old	28 (90.3%)	28 (71.8%)	0.073[b]
	>65 years old	3 (9.7%)	11 (28.2%)	
Gender	Male	17 (54.8%)	19 (48.7%)	0.638[b]
	Female	14 (45.2%)	20 (51.3%)	
Co-morbidities [c]	0	7 (22.6%)	6 (15.4%)	0.244 [a]
	1	10 (32.3%)	8 (20.5%)	
	2	9 (29.0%)	14 (35.9%)	
	3/4	2/4(19.4)	10/1(28.2%)	
Primary site	Right sided colon	4 (12.9%)	8 (20.5%)	0.689[b]
	Left-sided colon	16 (51.6%)	20 (51.3%)	
	Rectum	11 (35.5%)	11 (28.2%)	
Initial stage	Stage I-III/Stage IV with resectable metastases	10/2 (38.7%)	19/4 (59.0%)	0.091 [b]
	Stage IV with irresectable metastases	19 (61.3%)	16 (41.0%)	
Resection of primary lesion		23 (74.2%)	30 (76.9%)	1.000[b]
Exposure to adjuvant chemotherapy		9 (29.0%)	23 (59.0%)	0.016*[b]
Recurrence during or < 6 months after last dose of oxaliplatin in adjuvant setting		1 (3.2%)	7 (17.9%)	0.069 [b]
k/N-RAS mutation status	Wild type	18 (58.1%)	15 (38.5%)	0.148 [b]
	Mutant/ Unknown	13/0 (41.9%)	21/3 (61.5%)	
Exposure to anti-VEGF agents in 1st and 2nd lines		26 (83.9%)	29 (74.4%)	0.391[b]
Time to treat failure of 1st+2nd line, in months, median (range, 95% CI) [d]		26.9 (6.9-73.9) [23.0-30.8]	16.2 (2.9-68.8) [11.1-21.3]	0.013* [d]
Performance status on Day2	ECOG 1	16 (51.6%)	7 (17.9%)	0.000*[b]
	ECOG 2	15 (48.4%)	17 (43.6%)	
	ECOG 3-4	0	15 (38.5%)	
Metastatic sites on Day1	Solitary [e]	5/14/1 (64.5%)	11/6/2(48.7%)	0.230[b]
	Multiple [f]	1/10 (35.5%)	6/14 (51.3%)	
	Lung involvement	12 (38.7%)	19 (48.7%)	0.472[b]
	Liver involvement	22 (71.0%)	16 (41.0%)	0.016*[b]
	Peritoneal carcinomatosis	4 (12.9%)	9 (23.1%)	0.36[b]
Metastatic sites on Day 2	Solitary [e]	3/1/1/1 (19.4%)	3/2/0/0 (12.8%)	0.347[b]
	Multiple [f]	24/1 (80.6%)	31/3 (87.2%)	
	Lung involvement	22(71.0%)	26 (66.7%)	0.798 [b]
	Liver involvement	23(74.2%)	19 (48.7%)	0.049*[b]
	Peritoneal carcinomatosis	5 (16.1%)	13 (33.3%)	0.168[b]

Foot note: *p <0.05. [a]: by Wilcoxon rank-sum test. [b]: by Fisher's exact test or Chi-square test as appropriate. [c] age factor included while 6 points for mCRC excluded. [d] by log-rank test. [e]: Solitary metastases included lung only, liver only, and other solitary metastatic sites (infra-phrenic lymphadenopathy, or pelvis, or bone and soft tissue) only. Pelvic metastasis is defined as lesion involving pelvic wall, urinary bladder, uterus, cervix, vagina, or female adnexa contiguously. [f]: Peritoneum carcinomatosis was also regarded as multiple metastatic sites of an individual patient. Metastatic sites such as supra or infra-phrenic lymphadenopathy, pleural effusion, adrenal glands, spleen, and pancreas only appeared in accompany with metastases involving other sites instead of appearing as a solitary metastatic site of an individual.

Results

A total of 70 cases eligible for analysis were searched out. Among them, 31 cases had exposure to regorafenib in beyond 2nd-line setting. Comparison was made between these two groups of patients classified by exposure to regorafenib with respect to characteristics shown in Table 1. The regorafenib group had lower proportion of patients who had exposure to adjuvant chemotherapy (29.0% versus 59.0%, p=0.016), higher proportion of patients who had liver metastases on both Day1 (71.0% versus 41.0%, p=0.016) and Day2 (74.2% versus 48.7%, p=0.049), longer duration of median TTF_{1+2} (26.9 months versus 16.2 months) and lower proportion of patients with poorer performance status (Patients with ECOG PS 1/2/3-4: 51.6%/48.4%/0% versus 17.9%/43.6/38.5%, p=0.00) on Day 2. By the

Table 2: Reasons for not anti-VEGF therapy in the first and second line setting.

	Regorafenib group n=5 out of 31	Non-regorafenib group n=10 out of 39
Continuation of anti-EGFR treatment throughout 1st and 2nd line treatment	3	5
Conditions considered not suitable for anti-VEGF therapy such as severe cardiac disease, stroke, thrombosis, massive hemorrhage, colon perforation, persistent bowel fistula caused by CRC, uncontrolled nephropathy with large amount of proteinuria and renal failure demanding hemodialysis	2	5

Table 3: Factors with impact on Overall survival beyond 2nd-line analyzed with univariate cox regression.

Factors		Significance	Hazard ratio	95.0% CI for Hazard ratio	
				Lower bound	Higher bound
Group: Regorafenib vs. non-regorafenib in beyond 2nd line setting		0.000*	0.292	0.164	0.520
Primary site	Right sided colon as indicator	0.119			
	Left sided colon	0.148	0.607	0.308	1.195
	Rectum	0.068	0.565	0.305	1.044
Age as a continuous variable		0.137	0.983	0.960	1.006
Gender: male vs. female		0.558	0.861	0.522	1.421
CCI [a]	CCI 0	0.169			
	CCI1	0.134	1.824	0.831	4.002
	CCI2	0.879	1.289	0.604	2.754
	CCI3	0.091	2.318	0.999	5.376
	CCI4	0.168	0.430	0.180	2.388
Initial stage: de novo irresectable vs. radically resected		0.955	1.014	0.615	1.673
Primary lesion resection: not resected vs. resected		0.853	1.056	0.592	1.885
Recurrence during or <= 6 months after last dose of oxaliplatin in adjuvant setting, yes vs. no		0.186	1.662	0.783	3.525
Ras mutation positive or unknown vs. wild type		0.870	1.043	0.631	1.722
Metastatic sites on day1, multiple vs. solitary		0.935	0.979	0.590	1.626
Lung metastases on day1, presence vs. absence		0.068	0.607	0.355	1.038
Liver metastases on day1, presence vs. absence		0.829	0.945	0.565	1.580
Peritoneal metastases on day1, presence vs. absence		0.109	1.718	0.887	3.326
Metastatic sites on day2, multiple vs. solitary		0.423	1.308	0.679	2.519
Lung metastases on day2, presence vs. absence		0.007*	0.475	0.276	0.819
Liver metastases on day2, presence vs. absence		0.943	0.981	0.580	1.660
Peritoneal metastases on day2, presence vs. absence		0.035*	1.873	1.047	3.351
Exposure to bevacizumab and/or ziv-aflibercept in 1st and 2nd line settings		0.534	0.815	0.428	1.552
TTF_{1+2} as a continuous variable		0.009*	0.970	0.948	0.992
ECOG performance status on Day2	ECOG 0-1	0.000*			
	ECOG2	0.229	1.427	0.799	2.547
	ECOG3-4	0.000*	13.040	5.775	29.446

Foot note: *p <0.05. [a] age factor included while 6 points for mCRC excluded.

way, there were more patients who did not have exposure to anti-VEGF therapy in 1st plus 2nd-line treatment for mCRC in the non-regorafenib group (n=10, 25.6%) than in the regorafenib group (n=5, 16.1%). The reasons of these 15 patients for not receiving anti-VEGF therapy in 1st plus 2nd line treatments were listed in Table 2.

There was a median interval of 0.9 (range: 0.1 – 2.9) months between the combined failure of 1st plus 2nd line treatment and initiation of regorafenib. 15 cases (48.4%) had dosage reduction from initiating regorafenib or later on. The duration of taking regorafenib ranged between 14 and 459 days for individual cases. Median OS_{rego} was 5.9 months (95% CI 4.18-7.62) months.

As for the 39 cases who did not have exposure to regorafenib in beyond 2nd-line setting, the immediate reason of failing to receive regorafenib included (a) patients' preference for other antineoplastic treatment (n=7), (b) patients' preference for alternative therapy such as traditional Chinese medicine (n=10), (c) tumor associated complications hindering exposure to regorafenib (n=11), and (d) deterioration of performance status (n=11). Those patients (n=22 out

of 70, 31.4%) who did not have exposure to regorafenib due to the latter 2 reasons were regarded as truly ineligible for regorafenib in the beyond 2nd-line setting.

The regorafenib group was superior to the non-regorafenib group with regard to both median overall survival beyond 2nd-line (OS_{b2}) (8.0 versus 3.8 months, HR 0.292, 95% CI 0.164-0.520, p=0.000) (Figure 1a) and median overall survival of advanced disease (OS_{1+2+3}) (34.9 versus 18.9 months, HR 0.432 [95% CI 0.257-0.726], p 0.002) (Figure 1b). By means of univariate cox regression, among all the factors listed in Table 3, the following factors including (1) exposure to regorafenib in the beyond 2nd-line setting, (2) presence of lung metastases on Day 2, and (3) longer TTF_{1+2}, were found to have beneficial impact on OS_{b2}, while (1) presence of peritoneal metastases on Day 2 and (2) poorer ECOG PS (3-4 vs. 0-1 and 2) on Day 2 had adverse impact on OS_{b2}.

To identify the possible predictors of failure and ineligibility for receiving regorafenib in beyond 2nd-line setting, all the factors in Table 3 which did not emerge before Day2, namely Metastatic sites on Day2 (multiple vs. solitary), Liver/Lung/Peritoneal metastases on Day2 (presence vs. absence), and ECOG performance status on Day2, were excluded. Among the remaining ones, shorter TTF_{1+2} (Odds ratio (OR) 0.943, 0.895-0.994, p=0.029) and presence of peritoneal metastases on Day1 (OR 4.491, 1.171-17.222, p=0.029) were found to be associated with ineligibility for regorafenib. Meanwhile, absence of liver metastases on Day1 (OR 0.212, 0.069-0.650, p=0.007) and shorter TTF_{1+2} (OR 0.949, 0.913-0.986, p=0.007) were associated with failure of receiving regorafenib in the beyond 2nd-line setting.

Discussion

The eligibility criteria of CORRECT trial stipulated that patients should have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 at the start of the trial [3]. In post-marketing large scale trials, the enrollment criteria as to patients' performance status were not as stringent as in randomized controlled trials. For example, the proportion of patients who had ECOG PS>=2 among all the patients enrolled in the French Rebecca study [6], Japan PMS study [7] and CORRELATE study [8] was 10.6%, 10%, and 8% respectively. Selection of patients in this study eligible for regorafenib was at discretion of attending physicians. Among the 31 patients who took regorafenib, 15 (48.4%) had an ECOG PS of 2 after treatment failure of standard 1st and 2nd-line treatment for mCRC. Among the 48 patients who were considered actually eligible for regorafenib on Day2, the proportion of patients with ECOG PS 2 was even higher (n=27, 56.3%). This proportion was by far higher than the percentage of patients having ECOG PS >=2 in abovementioned large-scale studies [6-8].

As for the patients who had exposure to regorafenib, the median OS_{rego} of 5.9 (95% confidence interval 4.18-7.62) months was numerically comparable to the counterparts in randomized trial such as CORRECT (6.4 months) [3] or those in large scale open-label studies including REBECCA (5.6 months) [6], Japanese PMS (6.9 months) [7] and CORRELATE (6.45 months) [8]. In comparison with the group of patients (N=39) who did not receive regorafenib, the regorafenib group had a longer median overall survival calculated either from the failure of 2nd-line treatment (OS_{b2}) or from the diagnosis of mCRC (OS_{1+2+3}). In this retrospective study, the patients in the non-regorafenib group and those in the regorafenib group were inevitably unbalanced regarding multiple features (Table1). It is intuitive to assume that the (1) *shorter median duration of* TTF_{1+2}, and (2) *higher proportion of patients with ECOG PS 3-4 upon failure of 2nd line treatment* were associated with the inferior OS_{b2} of the non-regorafenib group relative to that of the regorafenib group, whereas the impact of (3) *higher proportion of patients who had exposure to adjuvant chemotherapy* and (4) *lower proportion of patients with liver metastases on both Day1 and Day2* in the non-regorafenib group on median OS_{b2} was still to be elucidated by cox regression.

As for the precedent treatment for mCRC, oxaliplatin-based chemotherapy was the preferred first-line therapy unless disease progression emerged during or immediately after adjuvant chemotherapy comprising oxaliplatin, whereas irinotecan-based chemotherapy was a common choice for second-line treatments according to institutional protocols. It has already been demonstrated that the sequence of chemotherapy (FOLFOX as first line and FOLFIRI as second line, or vice versa) does not influence overall outcome [14]. In the era of combinational treatment comprising chemotherapy and target therapy for mCRC, a phase 3 trial showed that FLOFIRI plus bevacizumab was non-inferior for progression free survival, compared with mFOLFOX6 plus bevacizumab, as the first-line treatment of mCRC [15]. Another study showed that chemotherapy (mFOLFOX6 or FOLFIRI) plus cetuximab and chemotherapy plus bevacizumab in first-line were equivalent in terms of overall survival among patients having KRAS wild type mCRC [16]. Except 3 cases for whom test for RAS mutation status turned out to be futile, all the cases in both the Regorafenib group and the Non-regorafenib group had definite K-RAS mutation status. The proportion of patients with KRAS and NRAS wild type tumor was numerically lower in the non-regorafenib group than in the regorafenib group, but the difference was nonetheless statistically insignificant (38.5% vs. 58.1%). All the patients with KRAS and NRAS wild type tumor received cetuximab and/or panitumumab before Day2, as stipulated in the enrollment criteria of this study. The percentages of patients who received anti-VEGF treatment (bevacizumab and/or ziv-aflibercept) in precedent treatment were 83.9% and 74.4% respectively in the Regorafenib and Non-regorafenib group, which were numerically lower than the corresponding percentage in REBECCA trial (92 %) [6], whereas much higher than the counterparts of the regorafenib (24%) and placebo (19%) arms in the CONCUR trial. Subgroup analysis of overall survival in CONCUR study showed that patients who were not exposed to a targeted biological treatment before the trial seemed to derive a greater benefit from regorafenib than did those who had received previous targeted drugs [4]. Among these 15 patients (Table 2.2) for whom anti-VEGF therapy was withheld in the 1st and 2nd-line treatment, 7 had various contraindications for bevacizumab and the remaining 8 patients having RAS wild type tumor just maintained cetuximab/panitumumab throughout the 1st and 2nd-line treatment. It was deemed theoretically futile to continue anti-EGFR antibody while switching chemotherapy regimen after failure of last line of treatment with anti-EGFR incorporated [17]. Nonetheless, there were other studies demonstrating improved prognosis of continuing cetuximab after disease progression during first line treatment for mCRC with cetuximab added to chemotherapy, especially for those

patients exhibiting early tumor shrinkage during first line treatment [18]. 2 out of the 7 cases with contraindication for bevacizumab and ziv-aflibercept received regorafenib which also targeted the VEGF mediated pathway. There was a retrospective study showed widespread use of bevacizumab among patients who had prior contraindications such as severe cardiac disease, thrombosis, hemorrhage, stroke, hemoptysis, or colon perforation [19]. The risk and benefit of using regorafenib for mCRC patients, despite a known risk of toxicities associated with above-mentioned contraindications, were still to be elucidated by larger scale of real-world study data.

Concerning the predictors for overall survival in the beyond 2nd-line setting, besides exposure to regorafenib, it is intuitive to perceive that longer prior TTF_{1+2} and poorer ECOG PS (3-4 vs. 0-1 but not 2 vs. 0-1, Table 3) on Day 2 exerted significant impact upon OS_{b2}. Patients with peritoneal metastases were more inclined to have hypoalbuminemia, ascites, bowel obstruction and perforation, therefore the disease deteriorated more rapidly. The reason for which patients with presence of lung metastases on Day 2 had longer OS_{b2} is still to be elucidated.

This study focused particularly on predictors for failure of and ineligibility for receiving regorafenib in the beyond 2nd-line setting. Presence of peritoneal metastases upon diagnosis of mCRC were found to be associated with ineligibility, while absence of liver metastases at the same time point were associated with failure of receiving regorafenib. Since patients with peritoneal metastases from mCRC were more predisposed to become ineligible for further salvage treatment after sequential failure of 1st and 2nd-line doublet chemotherapy with or without target therapy as utilized in our study and hence were deprived of the survival benefit brought by regorafenib, modified upfront chemotherapy schedule with regorafenib incorporated may prolong the overall survival of these patient with dismal prognosis. The phase II CORDIAL study investigating regorafenib plus modified FOLFOX as first-line treatment of metastatic CRC failed to reach its primary endpoint, with the objective response rate in patients receiving regorafenib and mFOLFOX6 intermittently showing little difference from that seen with standard therapy alone [20]. On the other hand, given the long median duration of treatment (9.9 months) in the regorafenib arm, the authors indicated that it would be interesting to explore the hypothesis that addition of regorafenib as maintenance therapy to standard treatment might help to prolong tumor control duration than might be achieved with standard upfront treatment alone. In combination with the findings in our study, patients with peritoneal metastases from mCRC might be able to derive the most survival benefit from maintenance therapy with regorafenib after achieving a clinical response to standard upfront doublet/triplet cytotoxic chemotherapy with or without target therapy.

Conclusion

In this study, 55.7% (39 out of 70) of the patients with mCRC failed to receive regorafenib as salvage treatment upon failure of standard 1st and 2nd line treatment while 31.4% (22 out of 70) of them were truly ineligible. Presence of peritoneal metastases upon diagnosis of mCRC was found to be associated with future ineligibility for regorafenib in beyond 2nd-line setting.

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