RESEARCH ARTICLE

First-Line Mono-Chemotherapy in Frail Elderly Patients with Metastatic Colorectal Cancer

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Abstract

Background: Unlike for fit elderly metastatic colorectal cancer (mCRC) patients, general approaches to initial treatment for the frail older mCRC patients are not clear. Our aim was to evaluate the efficiency and safety of first-line single-agent treatment in one such group. Materials and Methods: We retrospectively evaluated mCRC patients aged 70 or older with an Eastern Cooperative Oncology Group performance score of 2. They had no prior treatment and underwent first-line single-agent capecitabine or other monotherapies until disease progression or unacceptable toxicity. Results: Thirty-six patients were included. Most (n:28, 77.8%) were treated with capecitabine. One patient achieved a complete response and 5 patients had a partial response for an overall response rate of 16.6%. Twelve patients (33.3%) remained stable. Median progression free survival was 5 months (confidence interval (CI), %; 3.59-6.40) and median overall survival was 10 months (95 CI%; 8.1-11.8). Grade 3-4 toxicity was found in 6 patients (16.6%). Febrile neutropenia was not observed and there were no toxicity-associated deaths. Conclusions: Capecitabine is a safe chemotherapeutic agent with moderate activity for first-line treatment of older metastatic colorectal cancer patients with limited performance status.

Keywords: Capecitabine - monotherapy - elderly - colorectal cancer - metastasis

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Introduction

The principles of treating metastatic colorectal cancer (mCRC) in the elder patients are similar as in younger patients. However, in older individuals, who may have age-related organ dysfunction and medical comorbidity, we have to pay attention particularly to the risks of chemotherapy in terms of treatment-related toxicity and quality of life issues (Satram-Hoang et al., 2013). Side effects of cytotoxic drugs negatively impact clinical outcome and increases the complexity of cancer management in this population (Meulenbeld et al., 2007).

Treatment decisions in older patients should be based upon not only age, but also upon performance status, cytotoxicity of chemotherapeutics, and consideration of accompanying comorbidities (Nguyen et al., 2009). Fit elderly mCRC patients without any chronic disease and organ dysfunction, are appropriate candidates for intensive first-line treatment (Aparicio et al., 2009). They could be treated with combination chemotherapy even with additional moleculer drugs like bevacizumab and cetuximab (Souglakos et al., 2005; Kozloff et al., 2010; Vamvakas et al., 2010; Sastre et al., 2011; Vrdoljak et al., 2011; Benavides et al., 2012; Berretta et al., 2012; Jehn et al., 2012). However, general approach to initial treatment for the frail older mCRC patients is not clear. Clinicians usually prefer mono-chemotherapy [oral 5-fluorouracil (5-FU) derivatives, short-term infusional 5-FU/calcium folinate, irinotecan] because of its more favorable toxicity profile compared to combination schedules. If the patients' performance status has improved following treatment, then another drug may be added to its monotherapy. If not, these patients are candidates for palliative care (Aparicio et al., 2003; Francois et al., 2008; Obeidat et al., 2009; Kuboki et al., 2011).

Clinical studies generally underrepresented patients over 70 years. Few studies included elderly patients, but only with good performance status. So, our knowledge about the treatment of elderly comorbid mCRC patients is very limited. The aim of the present study was to evaluate the efficiency of mono-chemotherapies in a group of mCRC patients aged >70 with an Eastern Cooperative Oncology Group (ECOG) performance score (PS) of 2 (Oken et al., 1982).

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Materials and Methods

Patients' selection

We retrospectively reviewed the medical records of mCRC patients that were referred to 3 medical oncology departments between January 2005 and September 2012. Age, sex, staging, date of diagnosis, localization of metastasis, date of metastasis, cancer localization, histological findings, and all subsequent treatments (chemotherapy, radiation therapy, and surgery) were recorded. Eligibility criteria included: age ≥70 years; ECOG performance status 2; adequate hematologic (absolute neutrophil count $\geq 1.5\times10^9$/L, platelets $\geq 100\times10^9$/L), hepatic (total bilirubin ≤2.0×upper limit of normal [ULN], serum transaminases ≤3.0×ULN), and creatinine ≤1.5×ULN. Patients were excluded if they had received any prior chemotherapy for metastatic or recurrent disease and if they had a history of adjuvant chemotherapy or radiotherapy within 6 months before starting the present study. Informed written consent for the study was obtained from each participant. The study began following approval by the Academic Committee in oncology clinic.

Treatment details

Patients received single chemotherapy agent including irinotecan, oral 5-FU derivatives [capecitabine, tegafur/uracil (UFT)] or iv 5-FU/calcium folinate. Actual dosing of drugs given to patients evaluated in this study were irinotecan 180 mg/m^2, capecitabine 1250 mg/m^2, UFT 300 mg/m^2, leucovorin 400 mg/m^2, 5-FU 400 mg/m^2 iv bolus, 5-FU 2400 mg/m^2 24 hour infusion with a chemotherapy infusion pump.

Response evaluation and toxicity

Baseline radiologic tumor assessments and clinical examinations were performed before therapy initiation. Disease evaluation was carried out after 3-4 cycles of treatment or at the end of treatment by computed tomography scans of the abdomen, pelvis and thorax. Magnetic resonance imaging or bone scan were allowed when indicated. Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (Eisenhauer et al., 2009), regarding complete response, partial response, stable disease, and progressive disease. Patients were also evaluated for hematological and non-hematological toxicities and were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 (Trotti et al., 2003). The next cycle was not administered unless the granulocyte number was ≥1,500/mm^3, platelet number ≥100,000/mm^3, and all non-hematological toxicities resolved to grade ≤1.

Statistical analysis

All statistical analyses were performed using SPSS version 19.0 for Windows (Statistical Package for Social Sciences, Chicago, IL). p values <0.05 were considered statistically significant. All available variables are given as number and percentage, and results are expressed as mean±SD. Progression free survival (PFS) was calculated from the start of treatment to the first progression of disease or death from any cause. Overall survival (OS) was calculated from the start of treatment to the date of death or last follow-up. We censored the last clinical visit data for patients that died without known progression. The Kaplan-Meier method was used to estimate PFS, median follow-up and OS distributions, while each variable was investigated by a univariate analysis for OS and PFS.

Results

Clinical features

Among mCRC patients that were treated at our medical oncology department, 36 elderly frail patients treated with first-line mono-chemotherapy were included in the study. The sample comprised 22 males (61.1%) and 14 females (38.9%). The median patient age was 77 years (range, 70-93). Twenty-four patients (66.8%) had colon primary and 12 (33.2%) had a rectum or recto-sigmoid primary. Nearly almost all of the patients were diagnosed at metastatic stage (n:32, 88.9%), whereas only 4 patients had locally advanced disease. Baseline patient characteristics and treatment details are shown in Table 1.

Table 1. Baseline Patient Characteristics and Treatment Details

Characteristics		No.	(%)
No. of patients		36	
Sex	Male	22	(61.1)
	Female	14	(38.9)
Age, years	Median	77	
	Range	70-93	
Primary tumor site	Colon	24	(66.8)
	Rectum	6	(16.6)
	Colorectal	6	(16.6)
Stage at first diagnosis	Local regional	4	(11.1)
	Metastatic	32	(88.9)
No. of metastatic sites	1	8	(22.2)
	2	8	(22.2)
	>2	20	(55.6)
Metastatic sites	Hepatic	13	(36.1)
	Pulmonary	9	(25.0)
	Peritonitis carcinoma	6	(16.7)
	Lymph node	13	(36.1)
	Bone	2	(5.6)
	Other	5	(13.9)
Prior adjuvant therapy	Yes	2	(5.6)
	No	34	(94.4)
First-line chemoterapy	Capesitabin	28	(77.8)
	Tegafur/Uracil	3	(8.3)
	5-Fluorouracil/calcium folinate	2	(5.6)
	Irinotecan	3	(8.3)
Second line therapy	Yes	15	(41.7)
	No	21	(58.3)
Third line therapy	Yes	6	(16.7)
	No	30	(83.3)
Cetuximab treatment	Yes	2	(5.6)
	No	35	(94.4)

Table 2. Response Rates of the Patients

	N	(%)
Complete Response	1	(2.8)
Partial Response	5	(13.9)
Stable Disease	12	(33.3)
Progressive Disease	18	(50.0)
Objective Response (Complete+Partial)	6	(16.6)

Table 3. Univariate Analysis in Terms of Variables

		Overall Survival			Progression Free Survival		
		n	Hazard ratio (95% CI)	p	n	Hazard ratio (95% CI)	p
Sex (male *vs* female)		22 *vs* 14	1.45 (0.61-3.45)	0.386	22 *vs* 14	1.06(0.49-2.30)	0.869
Primary tumor site	(reference: Rectum)	6		0.473	6		0.3
	Colon *vs* rectum	24 *vs* 6	0.54 (0.16-1.84)	0.329	24 *vs* 6	1.43 (0.42-4.9)	0.564
	Colorectal *vs* rectum	6 *vs* 6	0.24 (0.20-1.50)	0.247	6 *vs* 6	0.68 (0.24-1.91)	0.473
Stage at first diagnosis	Local regional *vs* Metastatic	4 *vs* 32	0.94 (0.21-4.08)	0.936	4 *vs* 32	0.92 (0.27-3.12)	0.904
First-line therapy	Capecitabine *vs* Other	27 *vs* 9	0.68 (0.24-1.92)	0.47	27 *vs* 9	1.07 (0.46-2.45)	0.871
Metastases	Liver	23	0.37 (0.13-1.01)	0.054	23	0.49 (0.21-1.15)	0.104
	Lung	9	0.74 (0.30-1.82)	0.523	9	0.67 (0.27-1.62)	0.38
	Peritoneal	6	2.5 (0.73-8.53)	0.143	6	0.91 (0.34-2.43)	0.861
	Lymph node	13	0.71 (0.30-1.66)	0.434	13	0.93 (0.41-2.08)	0.871
	Other	6	0.60 (0.21-1.67)	0.329	6	1.53 (0.57-4.11)	0.393
Metastatic Site Number	<2 *vs* ≥2	18 *vs* 18	0.44 (0.18-1.08)	0.76	18 *vs* 18	1.90 (0.88-4.09)	0.98

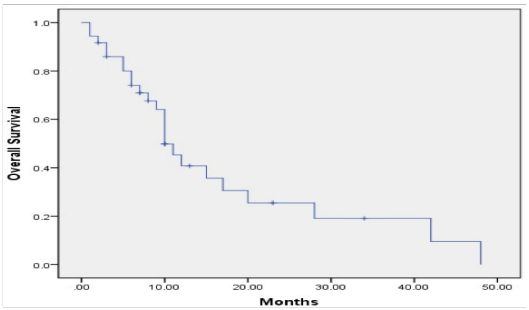

Figure 1. Overall Survival Curve of the Patients

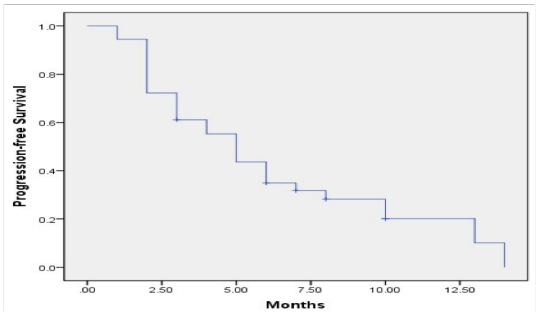

Figure 2. Progression Free Survival Curve of the Patients

Characteristics of metastasis

Among the patients, 2 previously received adjuvant therapy and developed metastasis during follow-up. The most frequent sites of metastases were; liver (13 patients, 36.1%), lung (9 patients, 25%), lymph nodes (6 patients, 36.1%), peritoneal (6 patients, 16.7%), bone (2 patients, 5.6%) and other metastatic lesions (adrenal, ovarian, etc.; 5 patients, 13.9%). The number of metastatic sites was more than 2 in most of the patients (n:20, 55.6%) while the others had either 1 or 2 metastases (n:8, 22.2%; n:8, 22.2% respectively).

Treatment patterns

The chemotherapies administered in the present study were; capecitabine (n:28, 77.8%), irinotecan (n:3, 8.3%), UFT (n:3, 8.3%) or iv 5-FU/calcium folinate (n:2, 5.6%). Treatments administered after first-line therapy were not specified as they were not able to be standardized. A high proportion (41.7%) of the patients treated with second-line chemotherapy regimen and 16.7% of the patients received third-line treatment. Two patients (5.6%) were subsequently treated with cetuximab following first-line treatment (Table 1).

Survival outcome and Toxicity

Fourteen percent of patients exhibited a confirmed partial response, 3% had a complete response, 33% had stable disease and 50% had progressive disease. At the time of this analysis, 18 patients (50%) developed disease progression, and 24 patients (66.7%) were died because of cancer-related factors (Table 2). Median PFS and OS of the patients was 5 months (confidence interval (CI), %; 3.59-6.40) and 10 months (95 CI%; 8.1-11.8) respectively (Figure 1, 2). The difference in median PFS and OS between the patients that were treated with capecitabine and other treatments was not significant (Table 3; p:0.87, p:0.47). In addition, the efficacy of mono-chemotherapy was compared in terms of tumor localization (colon, rectum or colorectal), localization of metastasis (hepatic, pulmonary, lymph nodes or others), metastatic site number (<2 or ≥2) and stage at first diagnosis (local regional or metastatic), but the differences were not significant either ($p<0.05$) (Table 3). Grade 3-4 toxicity was found in 6 patients (16.6%). Febrile neutropenia was not observed and there were no toxic deaths.

Discussion

Elderly patients constitute a subpopulation with higher risk of chronic diseases and are usually underrepresented in clinical trials. Additionally, both elderly and frail patients with poor performance status were not eligible for the randomized studies. Thus, our knowledge about the treatment of this subgroup is very limited. Initial aggressive treatment would not be generally recommended for them because of better tolerance of the single agents. Single agent cytotoxicity of drugs like 5-FU, capecitabine, UFT, irinotecan and cetuximab were also confirmed in improving the survival of their younger counterparts (Yoshimatsu et al., 2007; Duffour et al., 2010). For this reason, we retrospectively analyzed the toxicity and efficiency of mono-chemotherapy in the treatment of elderly frail patients affected by mCRC and found only a marginal benefit in terms of PFS and OS.

There is general agreement that frail older patients, those with significant comorbidity or an ECOG PS of 3 to 4, should be treated with palliative care. On the contrary,

active elderly patients without functional impairment should be treated in the same way as younger mCRC patients (Folprecht et al., 2004). Management of the patients who are neither frail nor fit is very complex and treatment requires individualized approach. Patients with mCRC who have a PS of 2 should be considered for chemotherapy, particularly if their PS decline is cancer related (Rosati et al., 2005). At the time of progression, patients initially treated with mono-chemotherapy and whose PS has improved could be treated with combination chemotherapy including irinotecan and oxaliplatin (Sastre et al., 2005; Arkenau et al., 2008). In our study, 41.7% of the patients were considered appropriate candidate for second-line treatment while 16.7% of the patients received third-line chemotherapy.

Capecitabine, an oral tumor-selective fluoropyrimidine, has been reported to have comparable efficacy with 5-FU based regimens in metastatic colorectal cancer. Capecitabine is routinely preferred for treatment of older patients with metastatic CRC due to convenience of oral dosing. Many trials consisting of elderly mCRC patients have established capecitabine monotherapy to be fairly well tolerated in elderly fit patients and have a similar efficacy with bolus 5-FU/LV regimens (Arkenau et al., 2005). However, it appears to be associated with more treatment-related adverse effects than infusional 5-FU/LV regimens. Besides, unlike infusional 5-FU-based therapy, a central venous access line and ambulatory infusion pump is not necessary for capecitabine treatment. So, capecitabine monotherapy is probably more toxic but more convenient than infusional 5-FU/LV in elderly patients with mCRC (Jackson et al., 2009; Hong et al., 2012).

MRC FOCUS2 study was one of the most comprehensive analyss regarding the efficiency of chemotherapy in elderly patients. In this study, patients were randomized into four groups: infusional 5-FU with calcium folinate; oxaliplatin and 5-FU; capecitabine; or oxaliplatin and capecitabine. Comparison of addition of oxaliplatin versus no addition did not reveal a significant improvement in PFS (median 5.8 months *vs* 4.5 months p:0·07) (Seymour et al., 2011). There was also no significant difference between capecitabine and 5-FU in terms of survival. The risk of having any high grade toxicity was not significantly increased with oxaliplatin but was slightly higher with capecitabine than with fluorouracil (Seymour et al., 2011). In another remarkable study, Feliu et al. analyzed mCRC patients >70 age or older who were considered ineligible for combination chemotherapy and treated them with capecitabine 1250 mg/m^2 twice daily for 14 of every 21 days. The median times to disease progression and overall survival were 7 months and 11 months respectively. The overall response rate was 24 percent, and grade 3 or 4 adverse events were detected only in 12 percent. Survival results and response rates of our patients were also similar to those studies (Feliu et al., 2005).

In conclusion, our study supports the first-line effectiveness of capecitabine monotherapy with manageable toxicity in elderly frail patients with advanced colorectal cancer. In older individuals, treatment decisions should be based on functional status, the presence of co-morbidities, and consideration of drug-specific toxicities that can be aggravated because of decreased functional reserve (Mitry et al., 2009). Knowledge and deeper research into treatment of the elderly patients will lead to more rational treatment approaches for them in the future.

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