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Duration of Chemotherapies in Phase III Studies on Metastatic Colorectal Cancer Treated With a Continuous Approach: A Seven-Year Survey

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Abstract

In last years, many phase III studies have addressed the role of chemotherapy or chemo/biotherapy in metastatic colorectal cancer (mCRC); most of these studies planned their treatment to be continued until disease progression or intolerable toxicity with the aim to obtain a long-term control of the cancer. However, the real duration of this approach might be significantly lower than planned. We made a survey to describe the real duration of chemotherapy in published phase III trials from January 2008 to December 2014. Twenty relevant publications were selected for a total of 48 treatment arms and of 24.475 patients. Median duration of chemotherapy in first-line studies ranged from 4,8 to 7,8 months; in second line from 2,4 to 5,2 months. Most common reasons of discontinuation were: progressive disease (PD), adverse events (AE) and patient request (PR). From 11.0% to 45.0% of patients discontinue treatment for toxicity or their request independently from the efficacy. PR was the third cause ranging from 4,6% to 26,0% of patients; in some studies, it overcame the AE-related withdrawals. Causes of PR for therapy discontinuation should be explored and analyzed to reduce the proportion of withdrawals in phase III studies.

Keywords: Colorectal cancer; Phase III studies; Toxicity; Chemotherapy; Survey

Introduction

The recent introduction of biologic therapies (cetuximab, bevacizumab, panitumumab) in combination with chemotherapy (fluoropirimidines, oxaliplatin, irinotecan), has extended median overall survival of patients with mCRC to two years and beyond [1]. Survival of 30 months and beyond can be reached in molecularly defined subpopulations [2]. As with other low-proliferating tumors (i.e. breast cancer), a sequential and continuous treatment approach using all active agents can obtain a long-term control of the disease and prolong survival [3]. Thus, for many patients, these developments have changed the therapeutic perspective of mCRC from an acute to a chronic condition. In last years, many randomized phase III studies have addressed the role of chemotherapy or chemo/biotherapy in mCRC; most of these studies planned their treatment to be continued until disease progression or intolerable toxicity. However, the real duration of this approach might be significantly lower than planned. How many patients are able to receive the planned treatment until progression or toxicity? Which is the burden of patient-related decisions in early discontinuation of therapies? We made a literature survey focused on this topic, to describe what is reported in published phase III studies.

Methods

We searched PubMed to describe the duration of chemotherapy in mCRC treated with chemotherapy planned until progressive disease or unacceptable toxicity (continuous approach). The upper data limit of January 2008 and the lower date limit of December 2013 were applied. The search strategy combined the following terms: (colorectal OR colon OR rectum OR colorectum OR) AND (cancer* OR carcinoma* OR neoplasm* OR tumor*). Thereafter, the search was limited to clinical, phase III, human studies. Ancillary or economic evaluations (as primary objective) subgroup or prognostic or interim/updated long-term analyses were excluded. Given the importance of AE in determining duration of treatments, phase III studies were selected using a 16-point AE reporting quality score (AERQS) based on the 2004 CONSORT extension [4]. Only studies with AERQS score >10 were selected. Other selection criteria were: prospective studies and first or second-line therapies. Selection was limited to publications in English language. The collected informations are reported in Table 1. When the information on treatment discontinuation was not reported in the text, it was extracted from tables and/or consort diagram. In anti-EGFR studies, when subgroup analyses were available, the description of data was restricted to KRAS WT-tumors.

Sixty-seven papers were selected. Reasons for exclusion were as follow: 15, AERQS ≤ 10; 7, ancillary; 3, economic evaluations; 6, subgroup analyses; 4, prognostic; 5, interim or updated long-term analyses; 7, more than one reason.

Results

Twenty relevant publications were selected from 2008 to 2014 for a total of 48 treatment arms and of 24.475 patients. Fifteen studies reported on first-line therapy; five on second-line. Duration of chemotherapy in first-line studies ranged from 4.8 to 7.8 months. In second line from 2.4 to 5.2 months. The three most common reasons of chemotherapy discontinuation were: progressive disease (PD), adverse events (AE) and patient request (PR). PD and AE were the major reasons of discontinuation in both first- and second-line

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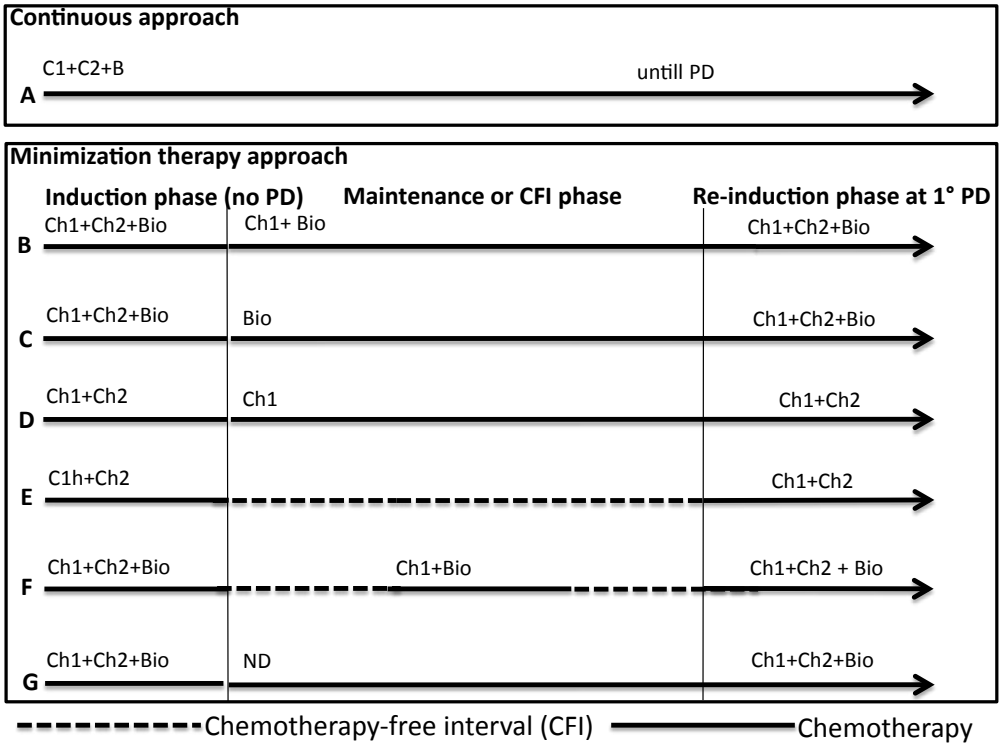
					Median duration of chemotherapy		Median Outcome (months)		Fist three most common reasons of discontinuation (%of patients)		
First Author	**Year**	**No. of patients**	**Line of treatment**	**Arms**	**No. of cycles**	**Months**	**PFS**	**OS**			
Rothenberg	2008	627	2°	Folfox	8,5	NR	4,8	12,5	PD (46.0)	AE (14.0)	NR
				Xelox	6	NR	4,7	11,9	PD (38.0)	AE (21.0)	NR
Cassidy	2008	2034	1°	Folfox (or Folfox/ Placebo)	10	NR	7,7	Pooled folfox arms: 19,6	NR	NR	AE (25.0)
				Folfox/Bev	12	NR	9,4		NR	NR	AE (30.0)
				Xelox (or Xelox/ Placebo)	7	NR	7,3	Pooled xelox arms: 19,8	NR	NR	AE (26.0)
				Xelox/Bev	8	NR	9,3		NR	NR	AE (31.0)
Saltz	2008	1401	1°	Folfox/Bev	NR	6,3	8,0	19,9	PD (29.0)	AE (30.0)	PR (9.0)
				Xelox/Bev							
				Folfox/Placebo	NR	5,8	9,4	21,3	PD (47.0)	AE (21.0)	PR (8.0)
				Xelox/Placebo							
Sobrero	2008	1298	2°	Cet/iri	NR	3,5	4,0	10,7	PD (67.5)	PR (7.7)	AE (6.5)
				Iri	NR	2,4	2,6	10,0	PD (68.0)	PR (6.6)	AE (4.8)
Haller	2008	628	2°	Irox	6	NR	5,3	13,4	PD (54.0)	PR (16.0)	AE (13.0)
				Iri	4	NR	2,8	11,1	PD (66.0)	AE (13.0)	PR (10.0)
Cunningham	2009	725	1°	Oxa/FU CIV Arm A	10 (information on total patients)	NR	A: 7,9	A: 15,9	PD (43.0)	AE (17.1)	PR (13.5)
				Folfox4 Arm A		NR					
				FU CIV Arm B		NR	B: 5,9	B: 15,2	PD (61.4)	PR (11.5)	AE (4.7)
				LV5FU2 Arm B		NR					
Van Cutsem	2009	1217	1°	Folfiri	NR	6	8,0	18,8	NR		
				Folfiri/Cet	NR	6	8,9	19,9			
Tol	2009	755	1°	Xelox/Bev	10	7	10,7	20,3	PD (54.0)	AE (25.9)	PR (6.1)
				Xelox/Cet	9	6	9,4	19,4	PD (48.5)	AE (29.6)	PR (7.5)
Hecht	2009	1053	1°	Folfox/PanBev	NR	NR	9,8	20,7	PD (29.0)	AE (22.0)	PR (16.0)
				Folfox/Bev	NR	NR	11,5	24,5	PD (26.0)	AE (24.0)	PR (21.0)
				Folfiri/PanBev	NR	NR	10,0	Not Estimable	PD (35.0)	AE (17.0)	PR (15.0)
				Folfiri/Bev	NR	NR	12,5	19,8	PD (27.0)	PR (26.0)	AE (6.0)
Douillard	2010	1183	1°	Folfox/Pan	FU 12; Oxa 11; Pan 10	NR	9,6	23,9	PD, AE, PR % or absolute number were not specified		
				Folfox	FU 12; Oxa 11	NR	8,0	19,7			
Peeters	2010	1186	2°	Folfiri/Pan	NR	NR	5,9	14,5	PD, AE, PR % or absolute number were not specified		
				Folfiri	NR	NR	3,9	12,5			
Maughan	2011	2445	1°	Folfox or Xelox	NR	7,2	8,6	17,9	NR		
				Folfox/Cet or Xelox/ Cet	NR	7,2	8,6	17,0			
Hecht	2011	1168	1°	Folfox/Vatalanib	NR	6,4	7,7	21,4	PD (51.2)	AE (22.3)	PR (14.7)
				Folfox/Placebo	NR	7,8	7,6	20,5	PD (66.5)	AE (12.1)	PR (10.1)
Schmoll	2012	1805	1°	Folfox/Ced	10	NR	9,9	22,8	PD (43.2)	PR (20.7)	AE (19.2)
				Folfox/Bev	12	NR	10,3	21,4	PD (42.7)	PR (18.6)	AE (18.4)
Madi	2012	2445	1°	Xelox vs Folfox	NR	NR	7,4 vs 8,8	15,4 vs 14,9	NR		
				Xelox/Cet vs Folfox/ Cet	NR	NR	7,4 vs 8,5	15,0 vs 14,9			
Van Cutsem	2012	1401	2°	Folfiri/Aflibercept vs	9	5,25	6,9	13,5	PD (50.4)	AE (26.9)	PR (13.7)
				Folfiri/Placebo	8	4,52	4,7	12,0	PD (72.2)	AE (12.2)	PR (7.4)
Hoff	2013	1076	1°	Folfox/Xelox/Ced 20 mg	9/10/6	NR	8,6	19,7	PD (56.7)	AE (22.5)	PR (10.1)
				Folfox/Xelox/Placebo	11/11/7	NR	8,3	18,9	PD (69.8)	AE (13.9)	PR (7.8)
Carrato	2013	768	1°	Folfiri/Sunitinib	NR	NR	7,8	20,3	PD (42.4)	AE (24.0)	PR (4.6)
				Folfiri/Placebo	NR	NR	8,4	19,8	PD (39.0)	AE (11.2)	PR (5.8)
Loupakis	2014	508	1°	Folfiri/Bev	12	NR	9,7	31,0	PD (30.3)	"Other reasons" (3.9)	AE (3.5)

				Folofoxiri/Bev	11	NR	12,1	25,8	PD (13.6)	AE (8.4)	Deaths (0.2%: 6 pts)
Heinemann	2014	752	1°	Folfiri/Cet	10	4,8	10,0	28,7	AE (15.0)	"Other reasons" (9.4)	
				Folfiri/Bev	12	5,3	10,3	25,0	AE (11.0)	"Other reasons" (6.7)	

PFS: Progression-Free Survival; OS: Overall Survival; Folfox: association of fluoropyrimidines and oxaliplatin; Folfiri: association of fluoropyrimidines and irinotecan; Cet: Cetuximab; Iri: irinotecan; Oxa: oxaliplatin; Bev: Bevacizumab; FU: fluorouracile; Pan: Panitumumab; Ced: Cediranib.
NR: Not reported; PD: Progressive Disease; AE: Adverse Events: PR: Patient Request.

Table 1: Descriptive analysis of selected studies.



Ch: chemotherapy; Ch1: favourable toxicity profile drug; Ch2: unfavourable profile (i.e. cumulative toxicity or specific toxicity); PD: progressive disease.
Bio: biologic drug of previuos schedule; ND: new drug

Figure 1: Common treatment strategy in mCRC.

studies. Notably, in phase III studies, from 11.0% to 45.0% of patients discontinue treatment for toxicity or their request independently from the efficacy. PR was the third cause of discontinuation ranging from 4.6% to 26.0% of patients and in some studies, it overcame the AE-related withdrawals (Table 1): this could be related to the desire of patients to have chemotherapy-free intervals.

Discussion

The most common treatment strategy in mCRC is the continuous administration of chemotherapy untill disease progression on intolerabe toxicity (Figure 1, line A). Therefore, from diagnosis onwards, an individual might spend most of his or her remaining life receiving continuous antitumor therapy, with the associated toxic effects, clinic visits, detriment to quality of life, and expense. The objective of the present survey was the description of real chemotherapy duration in phase III clinical trials of mCRC. No attempts were made to do meta-analysis because of treatments heterogeneity and strict selection of studies; furthermore, we cannot definitively rule out any relation between efficacy of treatments and time on therapy. However, duration of chemotherapy was quite homogeneous in first line studies reporting results with different chempotherapy schedules.

Why the patients discontinue treatments? There were no background data on factors predicting protocol adherence in phase III studies. It was reasonable to hypothesize that toxicity or progressions could account for the majority of withdrawals from a trial. However, in the present survey we found that PR (patient request) was the third cause of treatment discontinuation ranging from 4,6% to 26,0% of patients. Surprisingly, this phenomenon in some trials overcame the AE-related withdrawals. Thus, many patients treated with continuous approach chemotherapy, without progression of neither tumor nor serious adverse events; decide to stop the treatment and to remain in follow-up. Interestingly, in mCRC, patient request as a reason of discontinuation therapy may hide the occurrence of particular toxicities that may negatively impact on physical, emotional, and social aspects of quality of life of patients independently from their severity (skin toxicity with anti-EGFR agents, asthenia or diarrhea with irinotecan and/or fluoropirimidines, neuropathy with oxaliplatin).

Another detrimental effect of continuous therapy is psychological asthenia, a well-defined entity difficult to treat [5-7]. This aspect could be partially improved by managing patients in multidisciplinary teams involving psychologists. Other causes for study discontinuation could depend on logistics (transportation and/or mobilization difficulties, etc.) or personal/social reasons (loss of care-givers, change of opinion on protocol, etc.). Interestingly, in a series of 243 mCRC patients treated at our Institution with capecitabine, oxaliplatin and bevacizumab from 2008 to 2014 (median number of cycle: 7, median duration: 6,2 months) psychological asthenia due to continuous therapy (23 patients) was the first cause among patient requests of therapy discontinuation (article in press).

Notably, it is difficult to identify the balance between advantages of prolonged tretaments and drawbacks due to patients refusal of continue exposure to chemotherapy; in fact, in the larg part of phase III trials, patients who discontinue treatments are excluded from final outcome analyses and the real causes behind "patient request" are not analyzed. However, our data may offer a critical reflection: the proportion of patient discontinuing treatments in phase III studies of mCRC for their request is surprisingly too high. For this reason, in recent years, oncologistis have hypothesized different approaches to minimize time on therapy and alternative strategies have been explored (OPTIMOX1 –Figure 1, line D-, OPTIMOX2 and COIN studies –Figure 1, line E) [8-10] in order to reduce side-effects and improve quality of life and adherence to protocols. How to minimize time on chemotherapy with palliative intent without compromising efficacy (many examples of intermittent strategies are shown in Figure 1)? The question is completely open and should be explored in future phase III clinical trials *ad hoc* designed. Furthermore, causes of PR for therapy discontinuation should be explored and analyzed to reduce the proportion of withdrawals in phase III studies.

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