Longitudinal Patterns of Chemotherapy Use in Metastatic Colorectal Cancer

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Abstract

Purpose: Patients with metastatic colorectal cancer (mCRC) are increasingly exposed to multiple chemotherapy regimens. Insight into patterns of care in mCRC is crucial to understanding physician and patient decision making.

Methods: Patients with mCRC diagnosed between June 2003 and June 2006 were identified from one academic and nine community oncology practices in the southeastern United States. Demographic, disease, treatment, and toxicity data were abstracted by retrospective medical record review.

Results: After screening 738 medical records, 110 patients were determined eligible. Of these, mean age was 58 years (standard deviation, 12 years), 74% had stage IV disease at diagnosis, 39% were male, 53% were white, 26% were black, and 13% were age 70 years or older. As part of first-line mCRC chemotherapy, 100% of patients received regimens containing fluorouracil (FU), 87% received oxaliplatin (95% CI, 81% to 93%),

12% received irinotecan (95% CI, 6% to 18%), and 74% received bevacizumab (95% CI, 66% to 82%). The proportions of patients receiving subsequent lines of chemotherapy were: second line, 48% (n = 53); third line, 26% (n = 29); fourth line, 14% (n = 15); and fifth line, 5% (n = 5). From first- to third-line therapy, use of oxaliplatin and bevacizumab decreased, whereas irinotecan use increased. Among patients for whom therapy was discontinued, 29% experienced disease progression (PD), and 19% experienced toxicity; for 27%, no reason for discontinuation was documented. Of regimens containing oxaliplatin and irinotecan, 22% (n = 25 of 114) and 34% (n = 20 of 59) were discontinued because of PD, respectively. Of the same regimens, 19% (n = 21 of 114) and 20% (n = 12 of 59) were discontinued because of toxicity, respectively.

Conclusion: FU, oxaliplatin, and bevacizumab were most commonly used in first-line therapy for mCRC, despite data showing equivalency between regimens containing oxaliplatin and irinotecan. Use of oxaliplatin decreased and irinotecan use increased as treatment progressed beyond first-line therapy.

Introduction

New combination therapies have significantly improved survival in patients with metastatic colorectal cancer (mCRC). The addition of oxaliplatin or irinotecan to fluorouracil (FU) has improved overall survival, progression-free survival, and response rates compared with FU alone.¹⁻⁴ As survival with disease continues to increase, patients are exposed to an increasing number of chemotherapeutic agents and lines of chemotherapy.

Multiple agents and combination therapies available to patients with advanced CRC have provided an opportunity for individualization of care, whereby clinicians and patients can prioritize risks and benefits of comparable regimens.⁵ For example, in one study, two FU-based regimens were evaluated in the first and second lines of therapy for mCRC.⁶ Patients were randomly assigned to receive either FU, leucovorin, and irinotecan (FOLFIRI) or FU, leucovorin, and oxaliplatin (FOLFOX6) in the first line. On progression, patients were switched to the alternate regimen. Similar progression-free survival and response rates in the first and second lines of therapy were achieved with both regimens. However, toxicity profiles differed significantly between the first-line regimens. Patients receiving first-line FOLFIRI experienced greater frequencies mucositis, nausea/vomiting, and alopecia, whereas patients receiving first-line FOLFOX6 experienced more neutropenia and neurotoxicity. When regimens have equivalent efficacy but dif-

fering toxicity, patients and clinicians should have more freedom to select therapy on the basis of preference and patient circumstances. For example, a pianist could choose FOLFIRI to avoid sensory neuropathy.

With the addition of biologic agents such as bevacizumab—a monoclonal antibody directed against the vascular endothelial growth factor—and cetuximab and panitumumab—monoclonal antibodies targeting the endothelial growth factor receptor—various combinations and schedules have made management of mCRC extremely complex. Recent studies have continued to contrast efficacy between regimens containing these drugs, but to the best of our knowledge, no published study has examined community-based treatment patterns for mCRC in the United States. A better understanding of these treatment patterns could clarify how published findings from clinical trials are translated into practice. Given the proliferation of treatment options and lack of published data pertaining to community practice patterns, we undertook a longitudinal review to describe chemotherapeutic treatment patterns for mCRC.

Methods

Study Population

Using a population-based strategy, patients with CRC were retrospectively identified from one academic (Duke University

Medical Center, Durham, NC) and nine Duke University–affiliated community oncology practices. Eligible patients were adults with CRC diagnosed between June 2003 and June 2006 who received chemotherapy at a participating site. Their medical records had to contain at least 1 year of data on chemotherapeutic treatment plans and outcomes of treatments for mCRC. Patients had to have received as first-line chemotherapy either the combination of bolus FU, infusional FU, leucovorin, and oxaliplatin (FOLFOX) or FOLFIRI. Patients were excluded if they had been treated on a research protocol during the first or second lines of treatment. Informed consent was waived by the institutional review board. The research presented was conducted in accordance with the principles of the Declaration of Helsinki.⁷

Data Collection and Analysis

Lists of potential participants generated using the local tumor registry were prepared for each participating site. Tumor registries were searched for analytic and nonanalytic cases in which patients potentially met eligibility criteria. At sites that did not have tumor registries or where tumor registries included only analytic cases, billing or other available onsite databases were searched for potential participants. Case report forms were developed for medical record abstraction by trained abstractors.

Data were abstracted in two phases. Phase I was devoted to evaluation of CRC according to relevant quality metrics issued by national oversight agencies (eg, the National Comprehensive Cancer Network and ASCO). These data will be presented separately. Phase II focused on evaluation of longitudinal management of mCRC. These data are reported here. Data were abstracted with regard to patient sociodemographics; disease stage; chemotherapeutic regimens, doses, modifications, and treatment frequency; clinicians' reasons for choosing or discontinuing therapy; and adverse events. Data regarding toxicity and toxicity-related decision making will be presented separately. Data were double-entered from the paper questionnaire

Figure 1. Inclusion algorithm for participants. FOLFOX, fluorouracil, leucovorin, and oxaliplatin; FOLFIRI, fluorouracil, leucovorin, and irinotecan; mCRC, metastatic colorectal cancer.

Table 1. Patient Demographics and Clinical Characteristics

Characteristic	Patients (N = 110)	
	No.	%
Sex		
Missing/unknown	8	7.3
Female	59	53.6
Male	43	39.1
Ethnicity		
Missing/unknown	22	20.0
American Indian	1	0.9
Asian	1	0.9
Black	28	25.5
White	58	52.7
Method of payment		
Missing/unknown	24	21.8
Medicaid/Medicare	32	29.1
Other	54	49.1
Age at diagnosis, years		
Missing/unknown	24	21.8
< 70	72	65.5
≥ 70	14	12.7
Cancer site		
Unknown	3	2.7
Colon	82	74.5
Rectum	21	19.1
Rectosigmoid	4	3.6
Stage at diagnosis		
Missing/unknown	12	10.9
I	0	0
II	6	5.5
III	11	10.0
IV	81	73.6
Practice type		
Missing/unknown	3	2.7
Academic	9	8.2
Community	98	89.1

forms. Built-in validation parameters and electronic forms that mimicked the paper forms were used to reduce risk of data entry errors. A 10% visual data inspection, with 100% inspection of critical data elements, was completed. Analysis focused on descriptive statistics using SAS 9.1 (SAS Institute, Cary, NC).

Results

Of the 738 patients initially screened, 400 were eligible overall (Fig 1). Of these, 110 were eligible for phase II (Table 1). Of the 110 eligible patients, 39% were male, 53% were white, 29%

Figure 2. Percentages of chemotherapeutic regimens by (A) first, (B) second, and (C) third lines of treatment. CAPOX, capecitabine and oxaliplatin; FOLFIRI, FU, leucovorin, and irinotecan; FOLFOX, FU, leucovorin, and oxaliplatin; FU, fluorouracil.

had Medicare/Medicaid as a payer source, and 66% were younger than age 70 years. Mean age was 57.9 years. Men versus women were approximately equally likely to be treated with regimens containing FU (48% *v* 52%), oxaliplatin (48% *v* 52%), bevacizumab (45% *v* 55%), or irinotecan (41% *v* 59%). A majority of patients receiving any chemotherapy were younger than age 70 years (FU, 81%; bevacizumab, 82%; oxaliplatin, 85%; irinotecan, 79%).

A majority of patients (64%) were treated with FOLFOX-bevacizumab in the first line of treatment (Fig 2). Only six distinct

regimens were used. In the second line of treatment, FOLFIRI-bevacizumab was the most common regimen used (13% of patients), but much greater regimen variety was noted; 19 distinct regimens were used. In the third line of treatment, irinotecan plus cetuximab was the most common regimen (21% of patients); 14 distinct regimens were used. As treatment progressed from first to third line, use of bevacizumab, FU, and oxaliplatin decreased, whereas use of irinotecan increased (Table 2).

In the first line of treatment, regimens were infrequently used before approval by the US Food and Drug Administration (Table 3). Regimens were often used before data from phase III studies supporting use of these regimens were published, suggesting that oncologists were willing to treat patients on the basis of preliminary or phase II data. Bevacizumab was used in combination with chemotherapy after US Food and Drug Administration approval but before phase III study publication and recommendation by the National Comprehensive Cancer Network.

One patient was abstracted as having received FOLFOX plus bevacizumab and capecitabine. Because it is unlikely that this patient received FU and capecitabine simultaneously, one could infer that the patient was switched from FU to capecitabine, but this was not clear from medical record abstraction.

Reason for physician choice of regimen was abstracted from medical records when that information was available. Physician reason for choosing a particular regimen was poorly documented and therefore missing from the majority of medical records (65%). Of those records in which reason for therapy choice was documented, 10% attributed choice to treatment guidelines, 12% to perceived patient tolerability, 1% to patient preference, fewer than 1% to comfort or experience with the particular regimen, and fewer than 1% to patient comorbidities.

Reasons for ending therapy were documented by physicians more often than reasons for choice of therapy; only 27% of medical records were missing reason for chemotherapy discontinuation. At time of abstraction, 13% of patients were still receiving therapy. Of those records in which reason for therapy discontinuation was documented, 18% attributed ending of treatment to tolerability or toxicity, 29% to disease progression, 10% to completion of predetermined treatment course, 2% to patient preference, and fewer than 1% to physician preference. For one patient, death was given as reason for discontinuation of therapy.

Discussion

This community-based study reveals general treatment patterns for patients with mCRC. Oxaliplatin-based regimens were more commonly used in the first line of treatment than irinotecan-based regimens, and age played an important role in delivery of chemotherapy.

Table 2. Chemotherapy Administered by Treatment Line

Drug Included in Regimen	Treatment Line							
	All		First (n = 108)		Second (n = 53)		Third (n = 29)	
	No.	%	No.	%	No.	%	No.	%
Fluorouracil	162	85	108	100	37	70	17	59
Bevacizumab	115	61	80	74	26	49	9	31
Oxaliplatin	109	57	94	87	12	23	3	10
Irinotecan	51	27	13	12	23	43	15	52

NOTE. As treatment line progressed from first to third, use of bevacizumab, fluorouracil, and oxaliplatin decreased, whereas use of irinotecan increased.

Among those who were treated in our study, oxaliplatin-based regimens (eg, FOLFOX) were preferred over irinotecan-based regimens (eg, FOLFIRI). This pattern was noted despite data available during the study interval that demonstrated equivalent efficacy between the two regimens. Tournigand et al⁶ randomly assigned patients previously untreated for mCRC to receive either FOLFOX6 or FOLFIRI. On disease progression, oxaliplatin was replaced with irinotecan or vice versa. Similar response rates, progression-free survival, and overall survival in the first line of therapy were achieved with both regimens. Despite similar efficacy results, toxicity profiles were different for the two regimens. Patients experienced more neurotoxicity and hematologic toxicities with oxaliplatin and more febrile neutropenia, nausea/vomiting, mucositis, and fatigue with irinotecan.

Because a majority of medical records in our study did not contain documentation on why certain regimens were chosen, we can, for the most part, only speculate as to why oxaliplatin-based regimens were preferred over irinotecan-based regimens. First, oncologists might have been more familiar with oxaliplatin because of its success in the adjuvant setting.⁸ Irinotecan-based therapy, on the other hand, has been shown to be an ineffective adjuvant therapy when compared with FU alone.⁹ Second, the perceived toxicity profile of oxaliplatin-based regimens might be more acceptable to oncologists than that of irinotecan-based regimens. Along these lines, oncologists might be disinclined to use irinotecan because of worse outcome of irinotecan combined with bolus FU in comparison with FOLFOX.¹⁰ Ease of use should not have been a significant factor, because in both regimens, infusional FU is used, and 2-week cycles can be established.^{2,6} Other influences, including pharmaceutical industry marketing, cost, and reimbursement, might have also played a role.

The findings regarding physician treatment intent are incomplete, because 65% of medical records did not indicate why specific chemotherapeutic regimens were chosen over others. Of those in which treatment intent was documented, a majority indicated that oncologists made their choices on the basis of either perceived patient tolerability or treatment guidelines. Patients discontinued treatment most commonly as a result of disease progression and, secondly, as a result of treatment-related toxicity. Although these findings are limited by missing

data, they indicate that as patients live longer with mCRC, and as the number of drugs available to patients grows, toxicity plays an increasingly important role in selection of regimen.

A growing body of evidence supports an age bias against treating older patients, and this bias is additionally supported by our findings. A study of 6,959 patients with CRC identified through the Surveillance, Epidemiology, and End-Results–Medicare linked database demonstrated that older patients were significantly less likely to receive adjuvant chemotherapy, even after adjusting for presence of comorbid conditions.¹¹ In a study of California Cancer Registry data including 1,956 patients, Ayanian et al¹² found that patients age 85 years or older were significantly less likely than younger patients to receive adjuvant radiotherapy for rectal cancers. Schrag et al¹³ reported similar results in 1,670 patients with stage II and III rectal cancer identified through the Surveillance, Epidemiology, and End-Results–Medicare linked database. In this study, patients age 85 years or older were significantly less likely to receive radiotherapy or chemoradiotherapy, even after adjusting for degree of comorbidity.

Despite this evident bias, older patients who receive appropriate therapy tend to do as well as their younger counterparts. Goldberg et al¹⁴ conducted a retrospective, pooled analysis of four clinical trials evaluating adjuvant chemotherapy for CRC. The relative benefit of chemotherapy as measured by response rate and survival did not significantly differ in patients younger or older than age 70 years. Although this pooled analysis only included patients healthy enough for clinical trial participation, these important data suggest that numeric age by itself might not be as useful a tool in treatment-related decision making. Older age is also a negative predictor of whether a patient receives stage-appropriate chemotherapy in the usual care setting, even when controlling for comorbidity.¹⁵ In a single-institution study of 844 patients, Popescu et al¹⁶ found that elderly patients who received chemotherapy for mCRC did not experience worse toxicity or longer inpatient hospital stays compared with their younger counterparts.

The findings of our study are limited primarily by the design of retrospective medical record review. Understanding physician intent in selection of chemotherapeutic regimen was con-

Table 3. Evidence-Based Approach to Chemotherapeutic Regimens

First-Line Regimen by Year	Patients Receiving		FDA Approval	Recommendation in NCCN Guidelines	Phase III Publication Available
	No.	%			
FOLFOX					
2003	5	25	Yes	Yes	Yes, in 2000 ¹
2004	10	50		Yes	
2005	2	10		Yes	
2006	2	10		Yes, plus bevacizumab	
2007	1	5		Yes, plus bevacizumab	
FOLFIRI					
2003	1	33	Yes, in 2000	Yes	Yes, in 2000 ²
2004	0	0		Yes	
2005	2	67		Yes	
2006	0	0		Yes, plus bevacizumab	
2007	0	0		Yes, plus bevacizumab	
FOLFOX plus bevacizumab					
2003	0	0	Yes*		In 2008 ¹⁸
2004	27	40			
2005	34	50		Yes	
2006	6	9		Yes	
2007	1	1		Yes	
FOLFIRI plus bevacizumab					
2003	0	0	Yes*		Yes ¹⁷
2004	1	11			
2005	5	56		Yes	
2006	3	33		Yes	
2007	0	0		Yes	
Capecitabine, oxaliplatin, and bevacizumab					
2003	0	0	Yes, except capecitabine		In 2008 ¹⁸
2004	0	0			
2005	1	100			
2006	0	0		Yes	
2007	0	0		Yes	

Abbreviations: FDA, US Food and Drug Administration; NCCN, National Cancer Care Network; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; FOLFIRI, fluorouracil, leucovorin, and irinotecan.

* Bevacizumab approved in first line with any fluorouracil-based chemotherapy.

founded by missing data, in that reasons for selection or discontinuation of therapies were infrequently and inconsistently documented. Furthermore, because of agreements to maintain site-level anonymity of data, we were unable to compare treatment patterns between academic and community practices. Because the vast majority of our patient sample was treated in the community setting, even if such a comparison were to be presented, the data would likely be less than informative.

Despite these limitations, our study indicates a preference for oxaliplatin-based first-line therapy among community medical

oncologists. Furthermore, our findings support data from prior studies that demonstrate an age bias against treating older patients, regardless of type of chemotherapy. Prospective studies are needed for better understanding of physician intent in regimen selection for treatment of mCRC.

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References

- de Gramont A, Figer A, Seymour M, et al: Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 18:2938-2947, 2000
- Douillard JY, Cunningham D, Roth AD, et al: Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: A multicentre randomised trial. *Lancet* 355:1041-1047, 2000
- Maindrault-Goebel F, Louvet C, André T, et al: Oxaliplatin added to the simplified bimonthly leucovorin and 5-fluorouracil regimen as second-line therapy for metastatic colorectal cancer (FOLFOX6): GERCOR. *Eur J Cancer* 35:1338-1342, 1999
- André T, Louvet C, Maindrault-Goebel F, et al: CPT-11 (irinotecan) addition to bimonthly, high-dose leucovorin and bolus and continuous-infusion 5-fluorouracil (FOLFIRI) for pretreated metastatic colorectal cancer: GERCOR. *Eur J Cancer* 35:1343-1347, 1999
- Goldberg RM, Rothenberg ML, Van Cutsem E, et al: The continuum of care: A paradigm for the management of metastatic colorectal cancer. *Oncologist* 12:38-50, 2007
- Tournigand C, André T, Achille E, et al: FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: A randomized GERCOR study. *J Clin Oncol* 22:229-237, 2004
- World Medical Association: Declaration of Helsinki. <http://www.wma.net/ethics/b3.htm>
- André T, Boni C, Mounedji-Boudiaf L, et al: Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 350:2343-2351, 2004
- Saltz LB, Niedzwiecki D, Hollis D, et al: Irinotecan fluorouracil plus leucovorin is not superior to fluorouracil plus leucovorin alone as adjuvant treatment for stage III colon cancer: Results of CALGB 89803. *J Clin Oncol* 25:3456-3461, 2007
- Goldberg RM, Sargent DJ, Morton RF, et al: A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 22:23-30, 2004
- Schrag D, Cramer LD, Bach PB, et al: Age and adjuvant chemotherapy use after surgery for stage III colon cancer. *J Natl Cancer Inst* 93:850-7, 2001
- Ayanian JZ, Zaslavsky AM, Fuchs CS, et al: Use of adjuvant chemotherapy and radiation therapy for colorectal cancer in a population-based cohort. *J Clin Oncol* 21:1293-1300, 2003
- Schrag D, Gelfand SE, Bach PB, et al: Who gets adjuvant treatment for stage II and III rectal cancer? Insight from surveillance, epidemiology, and end results—Medicare. *J Clin Oncol* 19:3712-3718, 2001
- Goldberg RM, Tabah-Fisch I, Bleiberg H, et al: Pooled analysis of safety and efficacy of oxaliplatin plus fluorouracil/leucovorin administered bimonthly in elderly patients with colorectal cancer. *J Clin Oncol* 24:4085-4091, 2006
- Townsend C, Pond GR, Pelozo B, et al: Analysis of treatment practices for elderly cancer patients in Ontario, Canada. *J Clin Oncol* 23:3802-3810, 2005
- Popescu RA, Norman A, Ross PJ, et al: Adjuvant or palliative chemotherapy for colorectal cancer in patients 70 years or older. *J Clin Oncol* 17:2412-2418, 1999
- Fuchs CS, Marshall J, Mitchell E, et al: Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: Results from the BICC-C Study. *J Clin Oncol* 25:4779-4786, 2007
- Saltz LB, Clarke S, Díaz-Rubio E, et al: Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: A randomized phase III study. *J Clin Oncol* 26:2013-2019, 2008

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Commentary: Practice Patterns and Potential Impact on Quality Measures for a Practicing Physician

By Cathy Eng, MD, FACP, and Scott Kopetz, MD

Practicing physicians make multiple difficult treatment decisions daily. Several influences may affect choice of therapy, including consensus recommendations of the practice, ASCO or National Comprehensive Cancer Network guidelines, medical insurance coverage, geographic location of the practice, data from recently published or presented clinical trials, and familiarity with chemotherapeutic or biologic agent. Given the US Food and Drug Administration (FDA) approval of seven therapeutic agents in metastatic

colorectal cancer, various treatment combinations may be considered. Practice patterns vary significantly within individual practices and may be more pronounced when comparing community versus academic settings.

Zafar et al¹ have approached capturing community practice patterns in the population of patients with metastatic colorectal cancer, a challenging subject on which, to our knowledge, few data have been published. The objective of