Published in final edited form as:

Clin Colorectal Cancer. 2017 September ; 16(3): e205–e210. doi:10.1016/j.clcc.2016.09.005.

Chemotherapy Tolerance and Oncologic Outcomes in Patients With Colorectal Cancer With and Without Inflammatory Bowel Disease

Jordan Axelrad¹, Anuja Kriplani², Umut Ozbek³, Noam Harpaz^{2,4}, Jean-Frederic Colombel⁵, Steven Itzkowitz⁵, Randall F. Holcombe², and Celina Ang²

¹Division of Digestive and Liver Diseases, Department of Medicine, Columbia University Medical Center, New York, NY

²Division of Hematology and Oncology, the Icahn School of Medicine at Mount Sinai, New York, NY

³Department of Medicine Population Health Science and Policy, the Icahn School of Medicine at Mount Sinai, New York, NY

⁴Department of Pathology, the Icahn School of Medicine at Mount Sinai, New York, NY

⁵Division of Gastroenterology, Department of Medicine, the Icahn School of Medicine at Mount Sinai, New York, NY

Abstract

Inflammatory bowel disease (IBD) is a risk factor for colorectal cancer (CRC). We evaluated chemotherapy tolerance and oncologic outcomes from the medical records of patients with CRC with and without IBD. In this series, patients with CRC with IBD experienced more treatment alterations than those without IBD. Patients with stage IV CRC with IBD had shorter survival than patients without IBD.

Background—Inflammatory bowel disease (IBD), comprising Crohn disease and ulcerative colitis, is a risk factor for colorectal cancer (CRC). Chemotherapy toxicity may exacerbate IBD symptoms and vice versa, but data are limited. We evaluated chemotherapy tolerance and oncologic outcomes in patients with CRC with and without IBD.

Patients and Methods—Medical records of patients with CRC with and without IBD treated between 2008 and 2013 were reviewed. Where possible, patients were matched by age, sex, stage, and diagnosis year. Chemotherapy tolerance and survival outcomes were compared between patients with IBD and without IBD.

Results—A total of 158 subjects with CRC were included: 80 patients had IBD and 78 matched control patients did not have IBD. Between cases and controls, there were no significant

Address for correspondence: Jordan Axelrad, MD, MPH, Division of Digestive and Liver Diseases, Department of Medicine, Columbia University Medical Center, 630 W 168th St, Box 83, PH 7 West, Rm 319, New York, NY 10032, ja3064@cumc.columbia.edu.

Disclosure

The authors have stated that they have no conflicts of interest.

differences in demographic data, stage of CRC, and cancer treatments, with equivalent numbers of patients receiving surgery, radiation, and chemotherapy. Patients with IBD experienced more CRC treatment alterations than those without IBD (74% vs. 44%, $P = .03$), largely due to a higher frequency of treatment delays among patients with IBD. Differences in stage-specific 5-year overall survival (OS) and recurrence-free survival (RFS) in patients with and without IBD were not significant, except for stage IV patients with IBD who had significantly shorter OS than those without IBD. Patients with histologically active IBD did not require more chemotherapy alterations than patients with inactive IBD.

Conclusion—In this series, patients with CRC with IBD experienced more treatment alterations (mostly delays) than those without IBD. Patients with stage IV CRC with IBD had shorter survival than patients without IBD.

Keywords

Chemotherapy treatment alteration; Crohn disease; Overall survival; Recurrence-free survival; Ulcerative colitis

Introduction

Crohn disease (CD) and ulcerative colitis (UC) are chronic inflammatory conditions of the gastrointestinal tract. Together, inflammatory bowel disease (IBD) is estimated to affect more than 0.4% of Europeans and North Americans.¹ It is well recognized that patients with IBD are at an increased risk of developing colorectal cancer (CRC), thought to be the result of chronic intestinal inflammation.^{2–4} In a meta-analysis, quantitative estimates of CRC risk in UC have been reported to be 2% after 10 years, 8% after 20 years, and 18% after 30 years of disease.³ Studies on CRC in UC have noted a high concordance between risk of cancer with the location and extent of disease, with a standardized incidence ratio of 1.7 for proctitis, 2.8 for left-sided colitis, and 14.8 for pancolitis.⁵ Although more recent studies have demonstrated lower rates of CRC, 1.5 to 2.0 times greater than the general population in North America and in some European countries, all support the strong association between inflammation and cancer development.⁶

As the population of patients with IBD increases and ages, there is a predictable increase in the risk of sporadic and colitis-associated cancers, especially CRC. Many of these patients will require chemotherapy and/or radiation. Despite the high risk of CRC in IBD, very little is known regarding cancer treatment in patients with IBD.

Several small, retrospective and single-center studies have addressed the effects of cancer treatment on the course of IBD.^{7,8} However, very few have addressed cancer-specific outcomes, chemotherapy tolerance, and survival in patients with IBD. A study of 19 patients with IBD and gastrointestinal malignancy treated with 5-fluorouracil (5-FU)-based chemotherapy reported an increased risk of severe diarrhea ($n = 10$, 53%) resulting in discontinuation of therapy in 5 patients and dose reduction in another 5 patients.⁹ However, a substantial number of patients tolerated chemotherapy without increased difficulty, and patient age, type of IBD, dosing schedule of 5-FU, and the degree of IBD activity were not associated with toxicity.⁹ Another small study on 8 patients with IBD and gastrointestinal

malignancy reported diarrhea as the most common gastrointestinal adverse event, with 38% of patients experiencing more than 7 stools per day over baseline and/or fecal incontinence, all of which occurred in patients with CD.¹⁰ Neither of these studies had control groups without IBD, and neither commented on rates of disease recurrence or overall survival (OS).

Given the risk of CRC in patients with IBD, and limited data regarding chemotherapy tolerance and associated cancer outcomes, the aim of the present study was to evaluate chemotherapy tolerance and oncologic outcomes in patients with CRC with and without IBD.

Methods

Patient Population

The electronic medical records of patients with a diagnosis of pathologically confirmed CRC with and without a documented history of IBD treated at The Mount Sinai Hospital, New York, between 2008 and 2013, were reviewed. Patients with IBD (cases) and patients without IBD (controls) were matched by age (within 5 years), sex, stage, and diagnosis year (within 2 years).

Chart Review

Charts were reviewed for patient demographic information, including age at IBD diagnosis; IBD subtype; date of CRC diagnosis; stage of CRC; histologic IBD activity at CRC diagnosis; cancer treatment including surgery, radiotherapy, and chemotherapy; chemotherapy alterations for toxicity, such as treatment delays, discontinuations, dose modifications, and hospitalizations; date of last follow-up, death, or CRC recurrence diagnosis. Reasons for treatment alterations were recorded when available.

Study Objectives

CRC treatment characteristics and outcomes in patients with and without IBD were summarized. The primary objective was to compare the incidence of cancer treatment alterations due to toxicities in patients with CRC with and without IBD. Secondary objectives were stage-specific 5-year OS and recurrence-free survival (RFS) in patients with and without IBD. We also assessed the effect of histopathologic IBD activity on chemotherapy alterations.

Statistical Analyses

The variables are summarized using frequencies, and median and minimum-maximum values. Categorical variables were compared by using χ^2 or Fisher exact tests. Continuous variables were compared by using Mann-Whitney *U* test. OS and RFS were estimated with the use of Kaplan-Meier plots, and log-rank tests were used to compare the outcomes between patients with and without IBD. All reported *P* values are 2-sided. All analyses were performed in SAS v9.4 statistical software (SAS Institute, Cary, NC).

This study was performed with approval from the Icahn School of Medicine Institutional Review Board, with waiver of consent.

Results

A total of 158 subjects were included in this analysis. There were 80 patients with CRC and IBD. In terms of IBD subtype, 25 (31.25%) had CD and 55 (68.75%) had UC. There were 78 matched controls with CRC who did not have IBD. Between cases and controls, there were no significant differences in basic demographic data, stage of CRC, and cancer treatments with statistically equivalent numbers of patients receiving surgery, radiation, and chemotherapy for their CRC (Table 1). Molecular pathology data were available for 45 patients (28.5%) and there were no differences in mismatch repair protein expression, *KRAS* or *BRAF* mutation status between patients with and without IBD. Median duration of IBD at CRC diagnosis was 25 years (range 1–59), and of these patients, 51 (64%) had histologically active IBD at the time of their CRC diagnosis.

There were also no statistically significant differences in chemotherapy regimens. The patients with and without IBD received fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab, anti-EGFR agents, and regional chemotherapy at similar frequencies (Table 2).

Among patients in whom information was available regarding CRC treatment alteration, significantly more patients with IBD experienced CRC treatment alterations (23/31, 74%) than those without IBD (12/27, 44%; $P = .03$) (Table 3). This was largely due to a higher frequency of treatment delays among patients with IBD. The most frequently cited reason for treatment alteration was related to gastrointestinal side effects. Details for specific reasons noted in patient charts for treatment delays, discontinuations, dose modifications, and hospitalizations are listed in Table 3.

Although there were no statistically significant differences in stage I, II, and III-specific 5-year OS and RFS between patients with CRC with and without IBD (Table 4), there was a trend of worse survival in IBD. Among patients with stage IV CRC, 5-year OS was significantly shorter in patients with IBD compared with patients without IBD (19% vs. 50%, $P = .017$; Figure 1). Neither IBD activity status (quiescent vs. active) nor the duration of IBD was associated with the frequency of chemotherapy alterations.

Discussion

Few studies have examined the cancer treatment tolerance and outcomes in patients with CRC with IBD, and to date, none have compared this with a matched non-IBD population. In this single-center cohort study, patients with IBD experienced a higher frequency of alterations in cancer treatment compared with patients without IBD, mostly due to delays in their cancer treatment. Given the retrospective nature of this study, data regarding specific reasons for treatment alterations were limited, although gastrointestinal side effects appeared to be more frequently encountered in patients with IBD than without IBD. Moreover, several patients with IBD in this cohort were also noted to experience gastrointestinal fistula during their CRC treatment, none of which were noted in controls.

It has been postulated that the mere presence of underlying IBD yields gastrointestinal mucosa more vulnerable to the toxic effects of chemotherapy.¹¹ In this series, IBD activity,

based on histologic confirmation from endoscopic or surgical assessments, was not associated with a significant difference in treatment alteration. This is consistent with data from a previous study in which the degree of IBD activity was not significantly associated with the development of severe diarrhea with 5-FU chemotherapy.⁹ In addition, studies have demonstrated a therapeutic benefit of cytotoxic chemotherapies on the course of IBD, which may directly impact the relationship between IBD activity and specific gastrointestinal chemotherapy toxicities.⁷ However, histologic IBD activity may not reflect the clinical course of IBD, and prospective studies are required to validate this measure.

Although there exists no method for distinguishing gastrointestinal side effects of cancer treatment from IBD-associated complications, the present data suggest that gastrointestinal complications during CRC treatment in patients with IBD are secondary to exacerbation of IBD. However, future studies, ideally prospective in nature, are required to help address this. Expert opinion has suggested treating patients with IBD who experience diarrhea during chemotherapy with aminosalicylates (eg, mesalamine) and avoiding immunosuppressive drugs, such as corticosteroids, thiopurines, and tumor necrosis factor- α antagonists, to prevent profound hematologic toxicities.¹¹

In the present series, there were no significant differences in 5-year OS or RFS between patients with IBD and without IBD with stage I to III CRC. However, survival was shorter in patients with stage IV with IBD compared with patients without IBD. Our study is consistent with previous reports of shorter survival in patients with IBD compared with those without IBD.^{12–14} In a series of 33 patients with UC and CRC, 5-year OS was 39%, significantly less than the 59% 5-year OS rate in 133 sporadic CRC controls (hazard ratio 1.83, $P = .03$).¹² In all of these previous single-center series, patients were not matched by cancer treatment. In contrast, several other studies have demonstrated comparable OS rates in patients with IBD and patients with sporadic cancer.^{15–19}

There are several limitations to the current study inherent to its retrospective design. The observed association of IBD and treatment alterations and OS could be due to the presence of other factors that contribute to CRC development and to individualized decision-making in the management of cancer in patients with IBD. As both cases and controls received similar chemotherapies and rates of radiation, we did not examine the impact of specific chemotherapy regimens, chemotherapy dosing protocols, or radiation dosing protocols on specific toxicities. Furthermore, our definition of active IBD was limited to patients with histologic evidence for active disease at their CRC diagnosis, which may not have fully captured all patients with active IBD or clinically relevant IBD, as we did not include a clinical surrogate for this analysis. In addition, the relatively small sample size suggests that our retrospective data may not be generalizable to other clinical settings.

Despite these limitations, this is one of the largest studies examining the impact of IBD on cancer treatment tolerance and oncologic outcomes in CRC. Larger studies may help clarify the trend of worse survival in patients with IBD and stages I to III CRC. In addition, future prospective studies in patients with IBD with cancer may provide insights into the best treatment regimens that maximize therapeutic benefit, minimize toxicity, and optimally improve cancer outcomes.

Acknowledgments

This research was supported in part by the Chemotherapy Foundation.

References

1. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology*. 2012; 142:46–54. e42. quiz e30. [PubMed: 22001864]
2. Rutter MD, Saunders BP, Wilkinson KH, et al. Thirty-year analysis of a colonoscopic surveillance program for neoplasia in ulcerative colitis. *Gastroenterology*. 2006; 130:1030–8. [PubMed: 16618396]
3. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut*. 2001; 48:526–35. [PubMed: 11247898]
4. Ullman TA, Itzkowitz SH. Intestinal inflammation and cancer. *Gastroenterology*. 2011; 140:1807–16. [PubMed: 21530747]
5. Ekblom A, Helmick C, Zack M, et al. Ulcerative colitis and colorectal cancer. A population-based study. *N Engl J Med*. 1990; 323:1228–33. [PubMed: 2215606]
6. Beaugerie L, Itzkowitz SH. Cancers complicating inflammatory bowel disease. *N Engl J Med*. 2015; 372:1441–52. [PubMed: 25853748]
7. Axelrad JE, Fowler SA, Friedman S, et al. Effects of cancer treatment on inflammatory bowel disease remission and reactivation. *Clin Gastroenterol Hepatol*. 2012; 10:1021–7.e1. [PubMed: 22732273]
8. Rajca S, Seksik P, Bourrier A, et al. Impact of the diagnosis and treatment of cancer on the course of inflammatory bowel disease. *J Crohns Colitis*. 2014; 8:819–24. [PubMed: 24439392]
9. Tiersten A, Saltz LB. Influence of inflammatory bowel disease on the ability of patients to tolerate systemic fluorouracil-based chemotherapy. *J Clin Oncol*. 1996; 14:2043–6. [PubMed: 8683234]
10. Naito A, Mizushima T, Takeyama H, et al. Feasibility of chemotherapy in patients with inflammatory bowel disease-related gastrointestinal cancer. *Hepatogastroenterology*. 2014; 61:942–6. [PubMed: 26158146]
11. Goessling W, Mayer RJ. Systemic treatment of patients who have colorectal cancer and inflammatory bowel disease. *Gastroenterol Clin North Am*. 2006; 35:713–27. [PubMed: 16952747]
12. Aarnio M, Mustonen H, Mecklin JP, et al. Prognosis of colorectal cancer varies in different high-risk conditions. *Ann Med*. 1998; 30:75–80. [PubMed: 9556092]
13. van Heerden JA, Beart RW Jr. Carcinoma of the colon and rectum complicating chronic ulcerative colitis. *Dis Colon Rectum*. 1980; 23:155–9. [PubMed: 7379668]
14. Green S, Stock RG, Greenstein AJ. Rectal cancer and inflammatory bowel disease: natural history and implications for radiation therapy. *Int J Radiat Oncol Biol Phys*. 1999; 44:835–40. [PubMed: 10386640]
15. Delaunoy T, Limburg PJ, Goldberg RM, et al. Colorectal cancer prognosis among patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2006; 4:335–42. [PubMed: 16527697]
16. Sugita A, Greenstein AJ, Ribeiro MB, et al. Survival with colorectal cancer in ulcerative colitis. A study of 102 cases. *Ann Surg*. 1993; 218:189–95. [PubMed: 8342999]
17. Gyde SN, Prior P, Thompson H, et al. Survival of patients with colorectal cancer complicating ulcerative colitis. *Gut*. 1984; 25:228–31. [PubMed: 6698437]
18. Kiran RP, Khoury W, Church JM, et al. Colorectal cancer complicating inflammatory bowel disease: similarities and differences between Crohn's and ulcerative colitis based on three decades of experience. *Ann Surg*. 2010; 252:330–5. [PubMed: 20622662]
19. Ali RA, Dooley C, Comber H, et al. Clinical features, treatment, and survival of patients with colorectal cancer with or without inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2011; 9:584–9. e1–2. [PubMed: 21565283]

Clinical Practice Points

- Patients with IBD are at an increased risk of developing CRC, thought to be the result of chronic intestinal inflammation. As the population of patients with IBD increases and ages, there is a predictable increase in the risk of sporadic and colitis-associated cancers, especially CRC. Many of these patients will require cancer treatment.
- Our study was conducted to describe CRC treatment characteristics and outcomes in patients with and without IBD, to compare the incidence of cancer treatment alterations due to toxicities in patients with CRC with and without IBD, to calculate stage-specific 5-year OS and RFS in patients with and without IBD, and to assess the effect of histopathologic IBD activity on chemotherapy alterations.
- Consistent with some existing literature, our study showed that patients with IBD experienced more CRC treatment alterations than those without IBD, largely due to a higher frequency of treatment delays. Differences in stage-specific 5-year OS and RFS in patients with IBD trended to be shorter than those without IBD, with those with stage IV having statistically significantly shorter OS than those without IBD. Patients with histologically active IBD did not require more chemotherapy alterations than patients with inactive IBD.
- Our study is one of the largest examining the impact of IBD on cancer treatment tolerance and oncologic outcomes in CRC. Our data suggest that gastrointestinal complications during CRC treatment in patients with IBD are secondary to exacerbation of IBD. Prospective studies in patients with IBD with cancer may provide further insights into the best treatment regimens that maximize therapeutic benefit and minimize toxicity.

Figure 1. Stage-Specific 5-Year Overall Survival Between Patients With Colorectal Cancer With and Without Inflammatory Bowel Disease. Stages I, II, and III $P > .05$; Stage IV $P = .017$

Table 1

Baseline Characteristics in Patients With Colorectal Cancer With and Without Inflammatory Bowel Disease

	IBD, n = 80; 25 CD, 55 UC	Non-IBD, n = 78	P
Median age at CRC diagnosis, years	54 (24–92)	57 (27–93)	NS
Male, n (%)	48 (60)	47 (60)	
Female, n (%)	32 (40)	31 (40)	NS
Histologically active IBD at CRC diagnosis, n (%)			
Yes	51 (64)	N/A	N/A
No	20 (25)		
Unknown	9 (11)		
Median duration of IBD at CRC diagnosis, years	25 (1–59)	N/A	N/A
CRC stage, n (%)			
I	29 (36)	24 (31)	
II	17 (21)	17 (22)	
III	20 (25)	24 (31)	
IV	12 (15)	12 (15)	
Unknown	2 (3)	1 (1)	NS
CRC molecular characteristics, n (%)			
Mismatch repair protein expression			
Deficient	3 (4)	6 (8)	
Proficient	17 (21)	19 (24)	
Unknown	60 (75)	53 (68)	NS
K-ras			
Wild type	5 (6)	9 (12)	
Mutation	5 (6)	1 (1)	
Unknown	70 (88)	68 (87)	NS
BRAF			
Wild type	4 (5)	5 (6)	
Mutation	0 (0)	0 (0)	
Unknown	76 (95)	73 (94)	NS
Cancer treatment			
Surgery	74 (93)	75 (96)	
Radiotherapy	13 (31)	11 (26)	
Chemotherapy	43 (70)	40 (68)	NS

Abbreviations: CD = Crohn disease; CRC = colorectal cancer; IBD = inflammatory bowel disease; N/A = not applicable; NS = not significant; UC = ulcerative colitis.

Table 2

Systemic Chemotherapy Regimens in Patients With Colorectal Cancer With and Without Inflammatory Bowel Disease

Systemic Chemotherapy Regimens	IBD	Non-IBD
FOLFOX/CAPOX	24	24
FOLFIRI/irinotecan	8	8
5FU+LV/capecitabine	11	11
Bevacizumab	7	11
Cetuximab/panitumumab	3	2
Regorafenib	1	0
Intraperitoneal mitomycin-C	1	2
Hepatic arterial infusion floxuridine	1	2

Abbreviations: 5FU = 5 fluorouracil; IBD = inflammatory bowel disease; LV = leucovorin.

Table 3

Cancer Treatment Alterations in Patients With Colorectal Cancer With and Without Inflammatory Bowel Disease

	IBD, n = 80	Non-IBD, n = 78	P
Patients with known cancer treatment alteration data, n (%)	31 (39)	27 (35)	>.05
Any treatment alteration, n (%)			
Yes	23 (74)	12 (44)	
No	8 (26)	15 (56)	.03
Dose modification			
N	7	1	
Reasons noted	Diarrhea, peripheral sensory neuropathy, thrombocytopenia, mucositis, ileitis, abdominal pain	Diarrhea, hand-foot skin reaction	
Treatment delay			
N	8	4	
Reasons noted	Myelosuppression, body aches/pains, sepsis, diarrhea, enterocutaneous fistulae, bursitis, bowel obstructions, peripheral neuropathy	Folliculitis, myelosuppression, recurrent urinary tract infections	
Treatment discontinuation			
N	7	8	
Reasons noted	Severe acne, fluid retention, diarrhea, excessive weight loss, neutropenia, mucositis, peripheral sensory neuropathy, hepatotoxicity	Neuropathy, hypersensitivity reaction, hypertension, hyperbilirubinemia, failure to thrive, hand-foot skin reaction, renal failure	
Hospitalization			
N	6	5	
Reasons noted	Diarrhea, peritonitis, sepsis	Hypotension, renal failure, disseminated intravascular coagulation, sepsis	

Abbreviation: IBD = inflammatory bowel disease.

Table 4

Stage-Specific 5-Year Overall Survival and Recurrence Free Survival Between Colorectal Cancer Patients With and Without Inflammatory Bowel Disease

	IBD, n = 80	Non-IBD, n = 78	<i>P</i>
5-year OS, %			
I	88	100	NS
II	83	100	NS
III	41	75	NS
IV	19	50	.017
5-year RFS, %			
I	89	81	NS
II	59	83	NS
III	60	38	NS

Abbreviations: IBD = inflammatory bowel disease; NS = not significant; OS = overall survival; RFS = recurrence-free survival.