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ORIGINAL REPORT

Resolution of *Clostridium difficile*–Associated Diarrhea in Patients With Cancer Treated With Fidaxomicin or Vancomycin

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ABSTRACT

Purpose
Patients with cancer are at increased risk for *Clostridium difficile*–associated diarrhea (CDAD). Little is known about treatment response.

Patients and Methods
Two double-blind trials randomly allocated 1,105 patients with CDAD to fidaxomicin or vancomycin treatment (modified intent-to-treat [mITT]), and 183 of these had cancer. Univariate and multivariate post hoc analyses compared effects of treatment and patient characteristics on cure, recurrence, and sustained response after 4 weeks. Time to resolution of diarrhea (TTROD) was also evaluated.

Results
Patients with cancer had a lower cure rate and longer TTROD than patients without cancer. Recurrence rates were similar. Cure was more likely with fidaxomicin than vancomycin (odds ratio [OR] 2.0; $P = .065$), recurrence was less likely (OR = 0.37; $P = .018$), and sustained response more frequent (OR = 2.56; $P = .003$). Under vancomycin, median TTROD was longer in patients with cancer than in those without (123 *v* 58 hours; log-rank $P < .001$). With fidaxomicin, median TTROD was not significantly affected by presence of cancer (74 *v* 54 hours; log-rank $P = .145$). In the full mITT population, age, hypoalbuminemia, and cancer were inversely associated with clinical cure by multivariate analysis. Study treatment with vancomycin was a significant predictor of recurrence ($P < .001$). Within the cancer population, low albumin was negatively and fidaxomicin was positively associated with improved cure.

Conclusion
For patients with cancer, fidaxomicin treatment was superior to vancomycin, resulting in higher cure and sustained response rates, shorter TTROD, and fewer recurrences.

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INTRODUCTION

Clostridium difficile–associated diarrhea (CDAD, also known as CDI for *C difficile* infection) is an opportunistic infection occurring predominantly in hospitalized patients, although community acquisition has increased in recent years. Antibiotic exposure, advanced age, and comorbidity are independent risk factors for acquiring CDAD. CDAD can be self-limiting on removal of inciting antibiotics or may progress to serious and life-threatening fulminant colitis, ileus, or toxic megacolon. Antibiotic treatment choices have been predominantly metronidazole and vancomycin for the past three decades.[1] Recently, fidaxomicin was approved for the treatment of CDAD in the United States and in Europe.[2]

A recent study found that incidence of CDAD was 1.7 per 1,000 patient-days for oncology patients and 2.4 per 1,000 patient-days among hematopoietic stem-cell transplant patients, six- and nine-fold higher, respectively, than the rate for other hospitalized patients.[3] Depressed immune response, prolonged hospitalization, exposure to chemotherapy, and repeated antibiotic treatments contribute to an increased risk for CDAD among oncology patients.[4] Antibiotics and chemotherapy can each induce alterations of the fecal microbiome.[5-7] Additionally, chemotherapeutic agents promote inflammatory changes in the gut, intestinal necrosis, and anaerobic conditions, allowing proliferation of *C difficile*, whereas leakage of protein into the lumen can inhibit degradation of *C difficile* toxins.[4,8-10] Patients undergoing stem-cell transplantation are prone to gut graft-versus-host disease and are particularly vulnerable to CDAD, with consequent increased morbidity and mortality.[3,4,11]

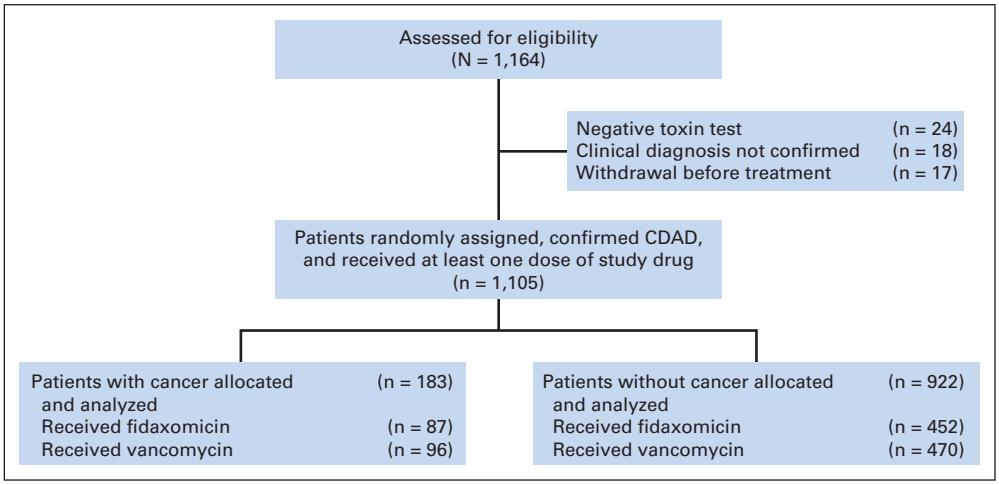

Fig 1. CONSORT diagram. CDAD, *Clostridium difficile*–associated diarrhea.

Studies have linked CDAD to increased mortality in patients with cancer, delay of chemotherapy or radiation treatments, and prolonged hospitalization.[11-13] Because the risk factors for CDAD persist, these patients are prone to recurrence. There is little information on response to CDAD therapy in patients with cancer. Metronidazole is often poorly tolerated by oncology patients because of nausea, oral and intestinal mucositis, and gastritis.[4] The use of vancomycin has raised concern about colonization with vancomycin-resistant *Enterococcus*.[14]

In a patient population from two controlled trials enrolling 1,105 patients with CDAD randomly assigned to treatment with fidaxomicin or vancomycin, we identified 183 patients with active solid tumors, hematologic malignancies, or both. Of these, 153 patients received at least 80% of their prescribed dose, or 8 days of therapy. Clinical cure, recurrence, sustained response at 4 weeks after completing CDAD therapy, and all-cause mortality were compared between patients with and without cancer and between treatment arms.

PATIENTS AND METHODS

Study Design and Patients

Two independent randomized, double-blind, controlled trials of identical design enrolled patients with CDAD. Study NCT00314951 was conducted from April 2006 to July 2008 in Canada and the United States,[15] and NCT00468728 was conducted from April 2007 to November 2009 in Canada, the United States, and Europe.[16] Eligible patients ≥ 16 years of age had more than three unformed bowel movements (UBM) in the 24 hours preceding randomization, CDAD confirmed by the presence of toxin A and/or B within 48 hours, and no more than one prior episode of CDAD in 90 days. Patients were randomly assigned to 10 days of oral treatment with fidaxomicin (200 mg twice daily with intervening placebo) or vancomycin (125 mg four times daily). Treatment with agents that might influence outcomes was prohibited, but four or fewer doses of metronidazole or vancomycin were allowed in the 24 hours preceding randomization, pending results of the stool toxin test. The full results of these studies are reported elsewhere.[15,16]

In this post hoc analysis, two subgroups were defined: patients with cancer and those without (Fig 1). Patients with solid tumors and/or hematologic malignancies were identified by system organ class and preferred term from active medical history entries of case report forms after coding by MedDRA version 10.0, by indications for concomitant medication entries, and by treatment-emergent adverse events. Malignancies were categorized as solid tumor or hematologic malignancy.

Analyses around these subgroups were conducted in the modified intent-to-treat (mITT) population (N = 1,105 overall, of whom 183 had cancer and 922 did not) and includes all randomly assigned patients with confirmed CDAD and receiving at least one dose of study medication. The population analyzed for safety comprised all patients receiving at least one dose of study drug.

The studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and were approved by each participating institutional ethics review board. All patients signed written informed consent before treatment.

Outcomes

Diarrhea was monitored by counts of UBM/24 hours during the 10 days of treatment and for 2 days after. Patients whose diarrhea resolved were followed for recurrence of symptoms for an additional 28 days following an end-of-therapy visit. Patients without recurrence during follow-up were evaluated at an end-of-study visit.

Clinical cure was resolution of diarrhea (≤ 3 UBMs/24 hours for 2 consecutive days maintained until end-of-therapy and 2 days after). In addition, an investigator assessed the success of therapy on the basis of clinical data signs and symptoms on day 10. Time to resolution of diarrhea (TTROD), which is another way to express cessation of diarrhea or cure, was time in hours from the first dose of study drug to the last UBM before 2 consecutive days with three or fewer UBMs, provided it was maintained until the end of therapy. Recurrence of CDAD was more than three UBMs/24 hours, positive stool toxin test, and need for re-treatment. Sustained clinical response (also known as global cure) was cure without recurrence.

Statistical Methods

Univariate analyses were performed using Pearson's χ^2 test or Fisher's exact test. TTROD was assessed by Kaplan-Meier survival analysis; the log-rank test was used for statistical comparisons. Multivariate analyses used logistic regression models adjusted for variables that included age, serum albumin (< 2.5 *v* ≥ 2.5 g/dL), concomitant antibiotics (yes *v* no), chemotherapy (yes *v* no), and study drug treatment (fidaxomicin *v* vancomycin); CIs and *P* values were derived by Wald statistics.

RESULTS

Patients

A total of 1,105 patients were enrolled, randomly assigned to treatment with fidaxomicin or vancomycin, had CDAD confirmed by

clinical signs and positive toxin assay, and received at least one dose of study drug. From this mITT population, 183 patients (16.6%) with active cancer were identified, 87 in the fidaxomicin treatment arm and 96 in the vancomycin arm; there was no difference in demographics and baseline characteristics between fidaxomicin and vancomycin groups (Appendix Table A1, online only). Compared with patients without cancer, proportionately more patients with cancer were male, inpatient, hypoalbuminemic, experiencing a first episode of CDAD, or treated with concomitant antibiotics. Proportionately more patients with cancer were leukopenic; 14.1% of patients with cancer had WBC less than 3.8×10^9/L, compared with 3.1% of patients without cancer.

Clinical Responses to Treatment

Patients with cancer had a lower rate of clinical cure (79.2%) than patients without cancer (88.6%; $P < .001$; Table 1). Consistent with the lower response rate, patients with cancer as a group had longer TTROD (Fig 2A; log-rank $P < .001$). Median TTROD was nearly doubled in patients with cancer (100 hours; 95% CI, 71 to 119 hours) versus those without cancer (55 hours; 95% CI, 53 to 58 hours; Appendix Table A2, online only). There was little effect of malignancy on recurrence; 21.4% of patients with cancer and 20.0% of patients without cancer had recurrence of CDAD ($P = .693$). Patients with cancer had a lower sustained response rate at 28 days after completing therapy (62.3% *v* 70.9%; $P = .020$). Although there were differences in response rates according to type of cancer (solid or hematologic) or whether patients received chemotherapy, sample sizes were too small to draw conclusions.

Initial response to fidaxomicin was relatively unaffected by cancer, but for patients treated with vancomycin, cure rates were lower for patients with cancer than those without cancer (Table 2). Cure rates were similar for patients without cancer treated with fidaxomicin (88.5%) or vancomycin (88.7%, $P = .913$). For patients with cancer, fidaxomicin treatment had a higher cure rate as compared with vancomycin treatment (85.1% *v* 74.0%, respectively (odds ratio [OR] = 2.0; 95% CI, 0.95 to 4.22; $P = .065$).

Median TTROD (Figs 2A through 2D; Appendix Table A2) in patients with cancer was 74 hours (95% CI, 54 to 103 hours) with fidaxomicin treatment and 123 hours (95% CI, 78 to 142 hours) with vancomycin treatment, and the difference in TTROD trends was significant (log-rank $P = .045$; Fig 2B). However, median TTROD was similar between treatment groups among patients without cancer: 54 hours (95% CI, 48 to 58 hours) versus 58 hours (95% CI, 54 to 72 hours), respectively. Thus presence of malignancy had a much greater impact on resolution with vancomycin treatment than with fidaxomicin treatment, as evident in Kaplan-Meier plots (Figs 2C and 2D); the difference in median TTROD between patients with and without cancer was 20 hours with fidaxomicin treatment (not significant; Fig 2C) and 65 hours with vancomycin treatment (log-rank $P < .001$; Fig 2D).

The likelihood of recurrence was roughly double for patients treated with vancomycin than those treated with fidaxomicin, regardless of whether patients had cancer (Table 2). Consequently, sustained response (cure without recurrence) was significantly higher with fidaxomicin than vancomycin, regardless of whether patients had cancer. However, because both cure and recurrence outcomes were improved in the fidaxomicin arm as compared with the vancomycin arm in patients with cancer, the relative odds of sustained response at 28 days in patients with cancer were more than 2.5-fold for fidaxomicin versus vancomycin (OR = 2.56; 95% CI, 1.37 to 4.77; $P = .003$; Table 2).

Multivariate Analysis

Multivariate analyses included presence or absence of cancer as well as clinical markers that might reflect severity of CDAD or consequences of malignancy or cancer treatments (Appendix Table A3, online only). In the full mITT population (with or without cancer, N = 1,105), variables of age, treatment arm, serum albumin, WBC counts outside the normal range (high or low), treatment with concomitant antibiotics, cancer (solid tumor, hematologic, or both), and treatment with chemotherapy were included in a logistic regression (Table 3). Treatment with fidaxomicin remained significantly associated with sustained response (OR = 1.86; $P < .001$) and inversely with recurrence (OR = 0.45; $P < .001$). The odds of clinical cure decreased with increasing age (OR = 0.98; $P = .012$), low serum albumin (OR = 0.35 for albumin < 2.5 g/dL; $P < .001$), receipt of concomitant antibiotics for other infections (OR = 0.69; $P = .092$), and presence of cancer (OR = 0.60; $P = .043$). Low WBC count ($<3.8 \times 10^9$/L) was associated with a lower, but not statistically significant, cure rate (OR = 0.41; 95% CI, 0.19 to 0.90; $P = .080$); only 24 (14.1%) of 170 patients were in this subgroup. Sustained response was associated with fidaxomicin treatment (OR = 1.86, relative to vancomycin; $P < .001$)

Table 1. Comparison of Outcomes in Patients With and Without Cancer

Characteristic	Cure			Recurrence			Sustained Response		
	No. of Patients	Total Patients	%	No. of Patients	Total Patients	%	No. of Patients	Total Patients	%
All patients	962	1105	87.1	194	962	20.2	768	1105	69.5
Patients without cancer	817	922	88.6	163	817	20.0	654	922	70.9
All patients with cancer	145	183	79.2	31	145	21.4	114	183	62.3
P (± cancer)		< .001			.693			.020	
Cancer subgroup*									
Solid tumor only	97	124	78.2	22	97	22.7	75	124	60.5
Hematologic only	31	37	83.8	3	31	9.7	28	37	75.7
Solid and hematologic	17	22	77.3	6	17	35.3	11	22	50.0
Receiving chemotherapy	27	33	81.8	4	27	14.8	23	33	69.7
Not receiving chemotherapy	118	150	78.7	27	118	22.9	91	150	60.7

*Solid tumor, hematologic, and solid and hematologic were exclusive categories.

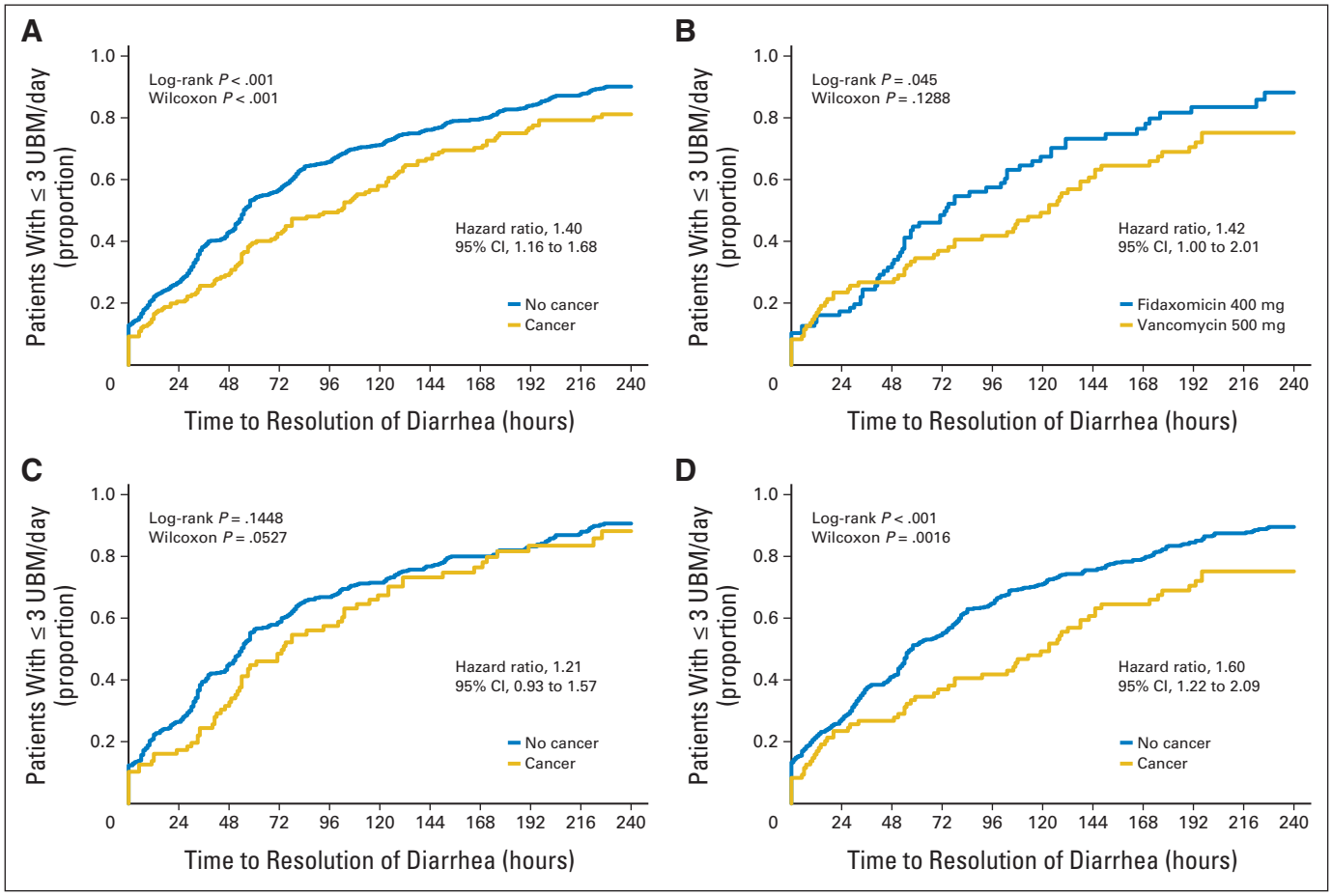

Fig 2. Time to resolution of diarrhea (TTROD) in patients with or without cancer. TTROD was time from first dose of study drug to last dose preceding 2 consecutive days with ≤ three unformed bowel movements (UBMs) per day maintained until end of therapy (modified intent-to-treat population). Statistical significance was determined by log-rank and Wilcoxon tests. (A) Patients with (n = 183) or without (n = 922) cancer, treatment groups combined. (B) Patients with cancer treated with fidaxomicin (n = 87) or vancomycin (n = 96). (C) Patients treated with fidaxomicin with (n = 87) or without cancer (n = 452). (D) Patients treated with vancomycin with (n = 96) or without cancer (n = 470).

and was inversely related to age (OR = 0.99; $P = .006$) and hypoalbuminemia (OR = 0.61; $P = .003$). Cancer and chemotherapy were not significantly associated with sustained response. No variable other than treatment with vancomycin was predictive of recurrence.

Safety

The safety population, comprising all patients who received at least one dose of study drug, included 192 patients with cancer, 95 in the fidaxomicin arm and 97 receiving vancomycin. Adverse event

Table 2. Outcomes of Treatment With Fidaxomicin Versus Vancomycin (mITT; N = 1,105)

Outcome	Fidaxomicin			Vancomycin				Fidaxomicin *v* Vancomycin		
	No. of Patients	Total Patients	%	No. of Patients	Total Patients	%	*P**	OR	95% CI	*P*†
Clinical cure										
Without cancer	400	452	88.5	417	470	88.7	.913	0.98	0.65 to 1.47	.913
With cancer	74	87	85.1	71	96	74.0	.065	2.00	0.95 to 4.22	.067
Recurrence										
Without cancer	57	400	14.3	106	417	25.4	< .001	0.49	0.34 to 0.70	< .001
With cancer	10	74	13.5	21	71	29.6	.018	0.37	0.16 to 0.86	.021
Sustained response										
Without cancer	343	452	75.9	311	470	66.2	.001	1.61	1.21 to 2.15	.001
With cancer	64	87	73.6	50	96	52.1	.003	2.56	1.37 to 4.77	.003

Abbreviation: mITT, modified intent to treat.
*Pearson χ^2 test for difference in proportions.
†The Wald χ^2 test was used to determine significance in odds ratios.

Table 3. Multivariate Analysis of Response to Treatment (mITT; N = 1,105)

Outcome Variable	Adjusted Odds Ratio	95% CI	*P*†
Clinical cure			
Age	0.98	0.97 to 1.00	.012
Serum albumin < 2.5 g/dL	0.35	0.23 to 0.54	< .001
WBC, low *v* normal range*	0.41	0.19 to 0.90	.080
WBC, high *v* normal range*	0.66	0.43 to 1.01	.898
Received concomitant antibiotics during treatment	0.69	0.44 to 1.06	.092
Treatment with fidaxomicin (*v* vancomycin)	1.20	0.81 to 1.79	.362
Received chemotherapy	1.18	0.42 to 3.31	.754
Cancer	0.60	0.37 to 0.98	.043
Recurrence			
Age	1.01	1.00 to 1.02	.105
Serum albumin < 2.5 g/dL	0.95	0.61 to 1.48	.805
WBC, low *v* normal range*	1.00	0.41 to 2.46	.840
WBC, high *v* normal range*	1.21	0.83 to 1.77	.498
Received concomitant antibiotics at any time	1.29	0.86 to 1.91	.215
Treatment with fidaxomicin (*v* vancomycin)	0.45	0.31 to 0.64	< .001
Received chemotherapy	0.88	0.26 to 2.94	.834
Cancer	1.04	0.62 to 1.75	.881
Sustained response			
Age	0.99	0.98 to 1.00	.006
Serum albumin < 2.5 g/dL	0.61	0.43 to 0.84	.003
WBC, low *v* normal range*	0.64	0.33 to 1.22	.362
WBC, high *v* normal range*	0.74	0.54 to 1.00	.700
Received concomitant antibiotics at any time	0.80	0.58 to 1.10	.163
Treatment with fidaxomicin (*v* vancomycin)	1.86	1.39 to 2.48	< .001
Received chemotherapy	1.19	0.50 to 2.84	.693
Cancer	0.77	0.52 to 1.14	.193

Abbreviation: mITT, modified intent to treat.
*WBC normal range, 3.8 to 10.7 × 10^9/L.
†The Wald χ^2 test was used to determine significance in odds ratios.

Table 4. Summary of TEAEs in Patients With Cancer by System Organ Class (safety population)

System Organ Class	Fidaxomicin 400 mg (n = 95)		Vancomycin 500 mg (N = 97)	
	No.	%	No.	%
No. of patients with ≥ 1 TEAE	81	85.3	81	83.5
Blood and lymphatic system disorders	13	13.7	8	8.2
Cardiac disorders	8	8.4	8	8.2
Congenital, familial, and genetic disorders	1	1.1	0	
Ear and labyrinth disorders	1	1.1	3	3.1
Eye disorders	2	2.1	1	1.0
GI disorders	42	44.2	32	33.0
General disorders and administration site conditions	26	27.4	25	25.8
Hepatobiliary disorders	1	1.1	2	2.1
Immune system disorders	2	2.1	1	1.0
Infections and Infestations	30	31.6	29	29.9
Injury, poisoning, and procedural complications	6	6.3	7	7.2
Investigations	19	20.0	12	12.4
Metabolism and nutrition disorders	21	22.1	21	21.6
Musculoskeletal and connective tissue disorders	10	10.5	6	6.2
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	8	8.4	5	5.2
Nervous system disorders	14	14.7	12	12.4
Pregnancy, puerperium, and perinatal conditions	1	1.1	0	
Psychiatric disorders	9	9.5	14	14.4
Renal and urinary disorders	10	10.5	8	8.2
Reproductive system and breast disorders	1	1.1	1	1.0
Respiratory, thoracic, and mediastinal disorders	19	20.0	15	15.5
Skin and subcutaneous tissue disorders	11	11.6	14	14.4
Surgical and medical procedures	0		1	1.0
Vascular disorders	11	11.6	6	6.2

Abbreviation: TEAEs, treatment-emergent adverse events.

rates were similar between treatment arms, with 81 (85.3%) of 95 patients receiving fidaxomicin having at least one adverse event and 81 (83.5%) of 97 patients receiving vancomycin having at least one adverse event (Table 4).

Mortality

There were 36 deaths (6.4%) among patients treated with fidaxomicin (n = 564) and 38 (6.5%) in the vancomycin treatment arm (n = 583) of the safety population of patients who received at least one dose of either study drug (Fig 3). Among the subgroup of patients with cancer, there were a total of 13 (13.7%) of 95 deaths resulting from any cause in the fidaxomicin group and 13 (13.4%) of 97 in the vancomycin treatment group. Five and three deaths, respectively, were associated with serious adverse events directly related to malignancies, specifically, acute myeloid leukemia, adrenal gland cancer, colon cancer, endometrial cancer, gallbladder cancer, lung cancer,[2] and renal cell carcinoma.

DISCUSSION

This subgroup analysis of a large combined study population from two phase III clinical trials allowed comparison of treatment outcomes in 183 patients with solid tumors, hematologic malignancies, or both, who acquired CDAD. Fidaxomicin, recently approved for treatment of CDAD in the United States, Europe, and Canada, was compared with vancomycin, the only other antibiotic approved by the US Food and Drug Administration for this disease. When compared with the 922 patients without known malignancies, patients with cancer had lower rates of clinical cure at end of treatment and sustained response 4 weeks later.

In this population, the recurrence rate was similar for patients with or without cancer. Some case studies of CDAD in patients with cancer have linked recurrences temporally with chemotherapy treatments but surprisingly not with courses of antibiotics.[17-19] In our study, only the treatment arm was significantly correlated with recurrence by multivariate analysis. Patients treated with fidaxomicin were half as likely to have a recurrence within 4 weeks of completing therapy than patients treated with vancomycin, after adjusting for cancer, hypoalbuminemia, low or high WBC count, treatment with other antibiotics, and age.

Rapid and sustained resolution of CDAD is particularly important for patients with cancer, because diarrhea often results in dose reductions or delays of chemotherapy or radiotherapy.[12,13] In patients with cancer, the median time to resolution of diarrhea was more than 2 days shorter with fidaxomicin (74 hours; 95% CI, 54 to 103 hours) than vancomycin (123 hours; 95% CI, 78 to 142 hours). Sustained response rates were significantly higher with fidaxomicin (73.6%) than vancomycin (52.1%; $P = .003$) in patients with cancer. A shorter time to resolution and sustained clinical response may minimize delays in cancer therapy and favorably influence outcomes.

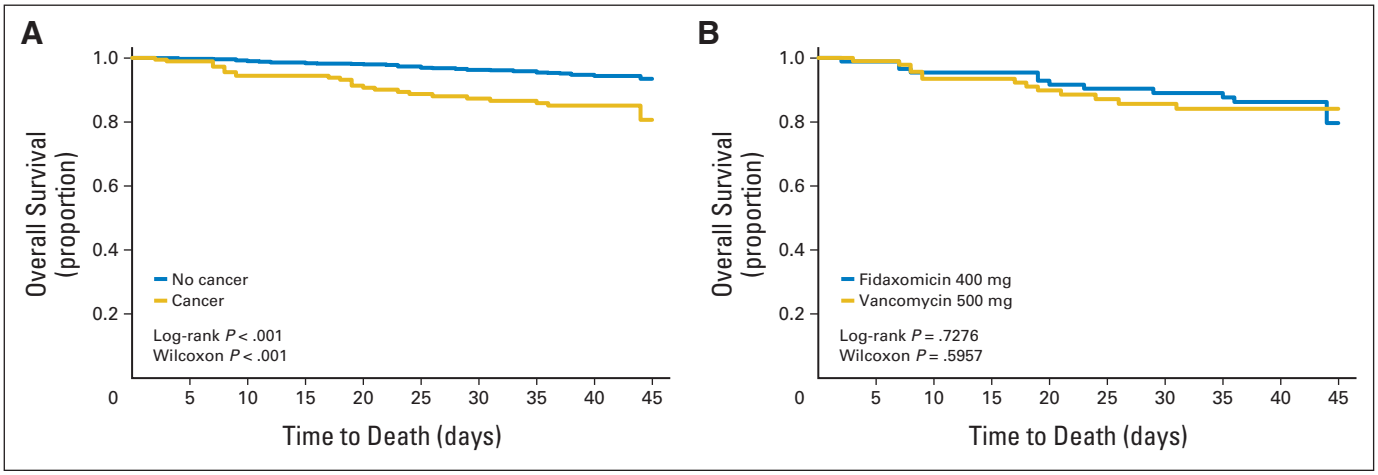

Fig 3. Survival analysis. (A) Kaplan-Meier curve for patients with cancer versus patients without cancer. (B) Kaplan-Meier curve for fidaxomicin versus vancomycin treatment.

Independent negative correlates of cure of CDAD were increasing age, the presence of cancer, treatment with antibiotics for other infections at the same time as CDAD treatment, and, most significantly, hypoalbuminemia. Serum albumin less than 2.5 g/dL was associated with a 65% reduction in the odds of clinical cure (OR = 0.35; $P < .001$) and a 39% reduction in the odds of sustained response (OR = 0.61; $P = .003$). Low serum albumin is most likely related to loss of protein through the ulcerated colon caused by CDAD. This explanation would account for the oft-noted relationship between low serum albumin and increased CDAD severity. A recent analysis of 2,761 patients with CDAD in a United Kingdom National Health Service Trust determined that cancer was a significant risk factor for 30-day mortality in patients ≥ 60 years of age (OR = 1.6) after adjusting for other comorbidities (cardiovascular, respiratory, and renal disease and cognitive impairment).[20] CDAD in patients undergoing allogeneic hematopoietic stem-cell transplant was associated with a greater risk of graft-versus-host disease and bloodstream infections, and those with severe CDAD had an increased risk of death within 6 months.[11]

A cautionary note should be included. This analysis was conducted post hoc as an exploration into the utility of fidaxomicin in the cancer population. The studies were not designed to look specifically at efficacy within patients with cancer, nor did the study attempt to balance or stratify around the different types of cancer. Despite these limitations, the results are promising and support the conduct of additional studies within cancer populations.

In summary, patients with cancer had significantly lower clinical cure and 28-day post-therapy sustained response rates than patients without cancer, and the differences were greater for patients treated with vancomycin than fidaxomicin-treated patients. Patients with cancer treated with fidaxomicin showed superiority in clinical cure and sustained response rates and lower incidence of recurrence than patients treated with vancomycin. Earlier resolution of diarrhea combined with a high probability of sustained response can potentially avoid delays in cancer therapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
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Collection and assembly of data: Kathleen Mullane
Data analysis and interpretation: Oliver A. Cornely, Mark A. Miller, Yin Kean
Manuscript writing: All authors
Final approval of manuscript: All authors

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Appendix

Table A1. Patient Demographics and Baseline Characteristics

	Any Cancer						No Cancer					
	Fidaxomicin (n = 87)		Vancomycin (n = 96)		All (n = 183)		Fidaxomicin (n = 452)		Vancomycin (n = 470)		All (n = 922)	
Characteristic	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Age, years												
Mean	65.6		67.1		66.3		61.5		61.9		61.7	
SD	14.8		14.0		14.4		17.9		18.1		18.0	
Median	68		70		69		63		63		63	
Range	19-89		21-93		19-93		18-94		19-94		18-94	
≤40	7	8.0	6	6.3	13	7.1	66	14.6	68	14.5	134	14.5
41-50	8	9.2	4	4.2	12	6.6	61	13.5	59	12.6	120	13.0
51-60	9	10.3	17	17.7	26	14.2	78	17.3	78	16.6	156	16.9
61-70	25	28.7	24	25.0	49	26.8	83	18.4	83	17.7	166	18.0
71-80	27	31.0	27	28.1	54	29.5	90	19.9	99	21.1	189	20.5
≥ 81	11	12.6	18	18.8	29	15.8	74	16.4	83	17.7	157	17.0
Exposure to study drug, days												
Mean	8.8		8.8		8.8		9.3		9.4		9.3	
SD	2.6		2.8		2.7		2.1		2.2		2.1	
Median	10		10		10		10		10		10	
Range	1-11		0-12		0-12		0-13		0-21		0-23	
Any cancer	87	100	96	100	183	100	0		0		0	
Solid tumor only	56	64.4	68	70.8	124	67.8						
Hematologic only	20	23.0	17	17.7	37	20.2						
Both	11	12.6	11	11.5	22	12.0						
Received chemotherapy	17	19.5	16	16.7	33	18.0						
Female	43	49.4	46	47.9	89	48.6	269	59.5	285	60.6	554	60.1
Inpatient	68	78.2	82	85.4	150	82.0	273	60.4	278	59.1	55	59.8
Prior episode of CDAD	10	11.5	12	12.5	22	12.0	78	17.3	78	16.6	156	16.9
Albumin < 2.5 g/dL	26/78	33.3	36/94	38.3	62	36.0	85/429	19.8	98/430	22.8	183	21.3
WBC < 3.8×10^9/L	12/78	15.4	12/92	13.0	24/170	14.1	15/403	3.7	11/408	2.7	26/811	3.1
WBC > 10.7×10^9/L	25/78	32.1	33/92	35.9	58/170	34.1	171/403	42.4	130/408	29.7	301/811	37.1
Concomitant antibiotics												
During treatment	27	31.0	37	38.5	64	35.0	79	17.5	85	18.1	164	17.8
During follow-up	33	37.9	33	34.4	66	36.1	83	18.4	95	20.2	178	19.3
At any time	41	47.1	44	45.8	85	46.4	114	25.2	124	26.4	238	25.8

Abbreviations: CDAD, *Clostridium difficile*–associated diarrhea; SD, standard deviation.

Table A2. Effect of Treatment on Time to Resolution (mITT)

	All		Fidaxomicin		Vancomycin		
Patient Group	Median TTROD (hours)	95% CI	Median TTROD (hours)	95% CI	Median TTROD (hours)	95% CI	Log-Rank *P**
Patients without cancer	55	53 to 58	54	48 to 58	58	54 to 72	.635
Patients with cancer	100	71 to 119†	74	54 to 103‡	123	78 to 142§	.045

Abbreviations: mITT, modified intent to treat; TTROD, time to resolution of diarrhea.
*Comparing fidaxomicin and vancomycin.
†Log-rank $P = .0003$, with versus without cancer.
‡Log-rank $P = .145$, with versus without cancer.
§Log-rank $P = .001$, with versus without cancer.

Table A3. Multivariate Analysis of Failure to Respond to Fidaxomicin and Vancomycin

Variable	Fidaxomicin (n = 539)			Vancomycin (n = 566)		
	Adjusted Odds Ratio	95% CI	*P*	Adjusted Odds Ratio	95% CI	*P*†
Age	0.98	0.95 to 1.01	.206	1.01	0.98 to 1.03	.686
Serum albumin < 2.5 g/dL	4.03	1.36 to 11.91	.012	3.07	1.36 to 6.96	.007
WBC, low *v* normal range*	0.26	0.04 to 1.67	.104	1.49	0.28 to 7.92	.557
WBC, high *v* normal range*	1.46	0.45 to 4.72	.131	0.83	0.37 to 1.87	.473
Received concomitant antibiotics during treatment	0.34	0.07 to 1.60	.174	1.61	0.70 to 3.73	.263
Received chemotherapy	0.16	<0.001 to 68.91	.555	2.43	0.49 to 11.95	.276
Cancer	0.50	0.10 to 2.46	.396	2.61	1.07 to 6.41	.036
Treatment duration (1-day decrease)	3.08	2.25 to 4.22	< .001	2.07	1.76 to 2.43	< .001

*WBC normal range, 3.8 to 10.7 $\times$ 10^9/L.
†The Wald χ^2 test was used to determine significance.