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Bezlotoxumab for the prevention of recurrent *Clostridioides difficile* infection for patients with cancer

Jaime A. Peña[a†], Cyril B. Mazhuvanchery[b†], Maria Julia Moura Nascimento Santos[b], Sidra Naz[b], Carolina Colli Cruz[b], Sharada Wali[b], Krishnavathana Varatharajalu[b], Pablo C. Okhuysen[c], Nancy N. Vuong[a⁂], Yinghong Wang[b⁂]

The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Abstract

Background Several clinical factors increase the susceptibility of cancer patients to *Clostridioides difficile* infection (CDI), often resulting in lower CDI treatment response rates and higher rates of recurrent CDI (rCDI). Bezlotoxumab, a monoclonal antibody targeting and neutralizing *C. difficile* toxin B, demonstrates a significant reduction in rCDI rates compared to standard of care alone in the general population. However, the effectiveness of bezlotoxumab in the cancer patient population requires further investigation. We assessed the incidence of rCDI within 90 days of bezlotoxumab treatment in patients with cancer.

Methods This was a single-center retrospective cohort study conducted at a tertiary care cancer center, including patients who received bezlotoxumab with standard-of-care antibiotics for CDI or rCDI between March 2016 and January 2023. Descriptive analyses were conducted.

Results A total of 177 patients with cancer who received bezlotoxumab were included. Most (76.8%) experienced <2 CDI episodes, whereas 23.2% experienced ≥2 episodes. Bezlotoxumab was administered a median of 10 days (interquartile range [IQR] 5-12.5) after symptom onset, and fidaxomicin was the most frequently used concurrent antibiotic (41.2%). Eleven patients (6.2%) underwent fecal microbiota transplantation before or after bezlotoxumab treatment. The overall 90-day rCDI recurrence rate was 6.2% (11 patients), with a median time to recurrence of 50 days (IQR 25-58).

Conclusions Bezlotoxumab demonstrated high efficacy in reducing rCDI within a 90-day period after administration, compared to rates in the non-cancer population. The findings suggest that administration of bezlotoxumab for rCDI prevention should be considered, given the improvement in the outcome of this high-risk group.

Keywords *Clostridioides difficile*, recurrent, prevention, cancer, bezlotoxumab

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†Co-first authors
⁂Co-senior authors

Correspondence to: Yinghong Wang, MD, PhD, Department of Gastroenterology, Hepatology & Nutrition, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., FCT13.6000, Houston, TX 77030, USA, e-mail: ywang59@mdanderson.org

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Introduction

Clostridioides difficile infection (CDI) remains a major health care challenge, mainly because of its high recurrence rates after standard-of-care antibiotic treatments [1]. Approximately 35% of patients with CDI develop recurrent CDI (rCDI), and this percentage can range from 13-41% for patients with cancer, whose immunosuppressed state makes them uniquely vulnerable [1-6]. Notably, 60% of individuals with rCDI experience multiple CDI episodes, resulting in cycles of prolonged hospitalizations, extended antibiotic use, and a significant increase in mortality rates [5,7,8].

The persistent risk for rCDI underscores the need for effective preventive strategies. Among recent advances,

bezlotoxumab, a monoclonal antibody targeting *C. difficile* toxin B, has promising potential in the prevention of rCDI in high-risk patient populations [9-13]. Clinical studies that included immunosuppressed individuals with CDI who received standard-of-care treatment demonstrated that bezlotoxumab can reduce the 12-week rCDI rate from 27.5% to 14% compared to placebo [13]. Additionally, patients who received bezlotoxumab had higher rates of sustained clinical remission (67.4% vs. 57%) and experienced significantly lower hospitalization rates within 30 days (5% vs. 15%) compared to patients who did not receive bezlotoxumab [13].

While these findings are encouraging, the use of bezlotoxumab for patients with cancer remains uncertain. The cancer patient population faces a unique confluence of risk factors for CDI, including the direct immunosuppressive effects of cancer, frequent and prolonged hospitalizations, repeated antibiotic exposure, microbiome disruption, and complications such as graft-versus-host disease [5,14,15]. These factors contribute to heightened susceptibility, lower response to standard-of-care treatment, and higher recurrence rates for patients with cancer [2,5,8,14,15].

Despite their heightened risk, the cancer patient population remains underrepresented in clinical trials focused on CDI prevention, which has left clinicians without sufficient evidence to guide the optimal management of rCDI in this vulnerable group [1,5]. The need for tailored preventive strategies is particularly urgent, as rCDI in immunocompromised patients exacerbates morbidity, prolongs hospital stays and strains health care resources [1,5].

The current study evaluated the use of bezlotoxumab to prevent rCDI for patients with cancer, addressing a critical gap in the literature. We aimed to provide real-world data on the efficacy and safety of this novel intervention in a patient population with complex medical needs who received treatment at a tertiary cancer center. We describe the treatment outcomes of such patients, providing noteworthy information for clinical practice and reinforcing care strategies for one of the groups at the most risk for rCDI.

[a]Division of Pharmacy, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA (Jaime A. Peña, Nancy N. Vuong); [b]Department of Gastroenterology, Hepatology and Nutrition, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA (Cyril B. Mazhuvanchery, Maria Julia Moura Nascimento Santos, Sidra Naz, Carolina Colli Cruz, Sharada Wali, Krishnavathana Varatharajalu, Yinghong Wang); [c]Department of Infectious Diseases, Infection Control and Employee Health, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA (Pablo C. Okhuysen)

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Materials and methods

Study design and population

This was a retrospective single-center cohort study that included adult patients with CDI who received standard-of-care antibiotics (e.g., vancomycin, fidaxomicin or metronidazole) and bezlotoxumab for the prevention of rCDI between March 1, 2016, and January 1, 2023, at our institution. The most recent episode of CDI/rCDI before bezlotoxumab was defined as the initial event. For inclusion, we identified adult patients (i.e., age 18 years or older) with cancer who: (1) were diagnosed with CDI or rCDI between March 1, 2016, and January 1, 2023, within 3 months of bezlotoxumab use; and (2) received bezlotoxumab for rCDI prevention. Patients with concomitant infectious gastrointestinal disorders were excluded. Fig. 1 illustrates the procedure for the selection of the patient population.

Clinical data

Demographic data, including age, sex and race, and oncologic data, including primary cancer type and stage, and cancer treatment, were collected from the electronic medical record. CDI-related parameters, including clinical symptoms, stool test results and antibiotic use, were reported. The CDI diagnosis was based on clinical presentation (i.e., defined by passage of 3 or more loose stools in 24 or fewer h) and diagnostic results (i.e., enzyme immunoassay [EIA] or DNA test results positive for CDI, or diagnosis of pseudomembranous colitis on endoscopy). rCDI diagnosis was defined as any new CDI episode after clinical cure of the original (i.e., clinical presentation associated with a CDI-positive DNA or/and EIA result 20 days or more after a resolved CDI case). As standard practice, all patients received oral, rectal or intravenous antibiotic treatment, as indicated

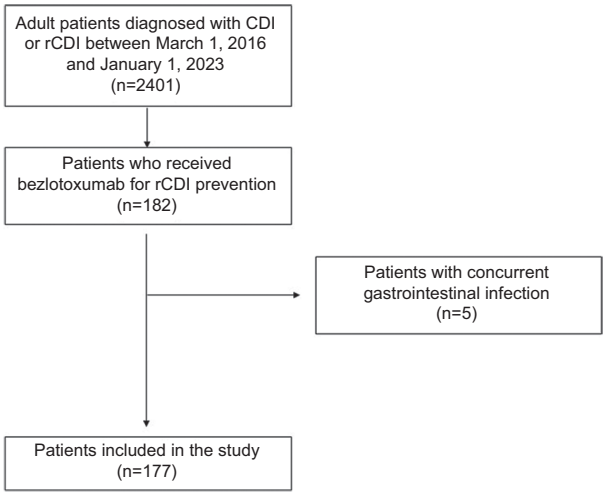

Figure 1 Patient selection diagram
CDI, Clostridium difficile infection; rCDI, recurrent C. difficile infection

(i.e., metronidazole, vancomycin or fidaxomicin), for CDI at the time of bezlotoxumab treatment.

Statistical analysis

The statistical analyses were descriptive in nature. Medians and interquartile ranges were used to summarize the distributions of continuous variables. Frequencies and percentages were used to summarize the distributions of categorical variables. SPSS, version 24, was used for the statistical analyses.

Results

Baseline demographics

177 patients met the predefined inclusion criteria. The cohort comprised mostly White (n=137, 77.4%) male (n=89, 50.3%) patients with a median age of 66 years (Table 1). About two-thirds of the cohort (n=120, 67.8%) had hematologic cancers (i.e., leukemia, lymphomas or myeloma) as their primary oncologic diagnosis. The all-cause mortality rate was 47.5% (n=84) and the median length of follow-up was 6.8 months. The findings are presented in Table 1.

Table 1 Baseline patient characteristics (N=177)

Characteristics	n (%)
Age, median (IQR), years	66 (54-73)
Sex	
Female	88 (49.7)
Male	89 (50.2)
Race or Ethnicity	
Asian	4 (9)
Black or African American	13 (7.3)
Hispanic or Latino	18 (10.2)
White	137 (77.4)
Cancer type	
Hematologic	120 (67.8)
Genitourinary	23 (13.0)
Head and neck	7 (4.0)
Gastrointestinal	7 (4.0)
Lung	5 (2.8)
Endocrine	4 (2.3)
Melanoma	1 (0.5)
Other	10 (5.6)
Cancer stage[1]	
I-II	9 (20.5)
III-IV	35 (79.5)
Type of cancer therapy received during the patient's last episode of CDI/rCDI treated with bezlotoxumab	
Chemotherapy	122 (68.9)
Immune-checkpoint inhibitors	12 (6.8)
Combined therapy[2]	15 (8.5)
No concurrent cancer treatment	28 (15.8)
All-cause mortality	84 (47.5)
Length of follow-up, median (IQR), months	6.8 (2.4-17.3)

[1]Only 44 patients had information about cancer staging in their medical record, so 44 was used as the denominator for this calculation
[2]Chemotherapy and immunotherapy
IQR, interquartile range; CDI, Clostridioides difficile infection; rCDI, recurrent Clostridioides difficile infection

Characteristics of CDI

Most patients (n=161, 91.0%) had positive DNA and EIA results for *C. difficile*, a smaller subset (n=12, 6.8%) had positive DNA but negative EIA results, while a few patients (n=4, 2.3%) did not undergo DNA or EIA testing, given their presumed CDI based on clinical presentation and colonoscopy findings of pseudomembranous colitis (Table 2). Most patients (n=136, 76.8%) had fewer than 2 previous CDI episodes. The median time from symptom onset to bezlotoxumab administration was 10 days (interquartile range [IQR] 5-12.5). As previous standard-of-care therapy, 35.0% of patients received fidaxomicin only, 22.6% received vancomycin only, and 42.4% received combined antibiotic therapies. Additionally, 6.2% of patients received a fecal microbiota transplantation (FMT) for CDI or rCDI within 8 weeks before or after bezlotoxumab administration (Table 2). rCDI within 90 days after bezlotoxumab administration occurred in 11 patients (6.2%), and 9 patients (5.1%) experienced recurrence within 8 weeks. No patients from the FMT cohort experienced rCDI within 90 days after bezlotoxumab administration. The median time to recurrence was 50 days (IQR 25-58). Four patients (2.3%) had post-bezlotoxumab rCDI requiring hospitalization, with a median length of stay of 20 days (IQR 10-51).

Standard-of-care treatment for initial CDI

A total of 124 patients received either vancomycin-based (n=49) or fidaxomicin-based (n=75) therapy for the initial CDI episode (i.e., the CDI episode before bezlotoxumab administration). Notably, patients in the vancomycin group had fewer CDI episodes before bezlotoxumab administration compared to patients in the fidaxomicin group (<2 episodes, 85.7% vs. 70.7%, P=0.026; ≥2 episodes, 12.2% vs. 29.3%, P=0.026). The length of antibiotic therapy tended to be longer in the vancomycin group (13 days [IQR 7-20] vs. 10 days [IQR 9-13], P=0.142). Hospitalization rates for the initial CDI were similar between groups (63.3% for the vancomycin group vs. 72.0% for the fidaxomicin group, P=0.306); however, the median length of hospitalization trended toward being longer for the vancomycin group (17 days [IQR 7.2-27.5] vs. 8.5 days [IQR 4-19], P=0.074).

Clinical remission at 30 days was achieved in most patients in both groups (93.9% for the vancomycin group vs. 88% for the fidaxomicin group, P=0.279). In both groups, rCDI rates within 90 days of bezlotoxumab administration were low (6.1% for the vancomycin group vs. 5.3% for

the fidaxomicin group; P=0.852). The median time to recurrence was greater in the fidaxomicin group than in the vancomycin group (35 days [IQR 15.5-70] vs. 17 days [IQR 7.2-27.7]), but the difference was not statistically significant (P=0.724). No significant differences were observed in re-hospitalization rates (66.7% for vancomycin vs. 75% for fidaxomicin, P=0.632) or all-cause mortality rates (42.9% for vancomycin vs. 50.7% for fidaxomicin, P=0.395) between the 2 groups.

Table 2 Clinical characteristics of patients with BZL-related CDI/rCDI (N=177)

Characteristics	n (%)
Number of CDI episodes 180 days before BZL initiation, median (IQR)	1 (0-1)
<2	136 (76.8)
≥2	41 (23.2)
Presenting symptoms[1]	
Diarrhea	176 (99.4)
Abdominal pain	100 (56.5)
Fever	87 (49.2)
Blood or mucus in stool	33 (18.6)
Laboratory results[1]	
CDI-positive DNA and EIA results	161 (91.0)
CDI-positive DNA and CDI-negative EIA results	12 (6.8)
No testing data[2]	4 (2.3)
Time from start of symptoms to BZL, median (IQR), days	10 (5-12.5)
Anti-CDI/rCDI treatment[1]	
Fidaxomicin	62 (35.0)
Vancomycin	40 (22.6)
Vancomycin and fidaxomicin	40 (22.6)
Fidaxomicin and metronidazole	13 (7.3)
Vancomycin and metronidazole	9 (5.1)
Vancomycin, fidaxomicin, and metronidazole	13 (7.3)
FMT[3]	11 (6.2)
Hospitalization[1]	124 (70.1)
Length of hospitalization, median (IQR), days	15 (7-32)
Outcome	
rCDI within 90 days of BZL treatment	11 (6.2)
rCDI within 90 days of BZL and FMT treatment	0 (0)
rCDI within 8 weeks after BZL	9 (5.1)
Time to rCDI, median (IQR), days[4]	50 (25-58)
Hospitalization for rCDI[4]	4 (2.3)
Length of hospitalization for rCDI, median (IQR), days[4]	20 (10-51)

[1]During the patient's last BZL-related CDI or rCDI episode
[2]These 4 patients had presumed CDI owing to a lack of EIA or DNA testing results, previous history, and colonoscopy findings of pseudomembranous colitis
[3]Within 8 weeks before or after bezlotoxumab treatment administration
[4]Within 90 days after bezlotoxumab treatment administration
BZL, bezlotoxumab; CDI, Clostridioides difficile infection; rCDI, recurrent C. difficile infection; DNA, C. difficile toxin gene testing; EIA, C. difficile toxin enzyme immunoassay; FMT, fecal microbiota transplantation; IQR, interquartile range

Factors associated with post-bezlotoxumab rCDI

A univariate analysis evaluated factors associated with rCDI after bezlotoxumab administration among 11 patients (Table 3). No significant association was found between rCDI and the number of previous rCDI/CDI episodes before bezlotoxumab administration (odds ratio [OR] 0.7, 95% confidence interval [CI] 0.202-3.125; P=0.748), time to intervention (OR 0.9, 95%CI 0.897-1.062; P=0.571), length of antibiotic therapy (OR 1.0, 95%CI 0.995-1.0; P=0.552), length of hospitalization for the initial CDI event (OR 1.0, 95%CI 0.991-1.014; P=0.606), combined versus single antibiotic therapy (OR 1.5, 95%CI 0.389-5.963; P=0.545) or FMT (OR 0.2, 95%CI 0.049-1.383; P=0.114). Among cancer characteristics, hematologic cancers had lower odds of rCDI compared to having solid cancer (OR 0.4, 95%CI 0.093-2.128; P=0.310), and advanced-stage cancer (stage III-IV) had higher odds of rCDI compared to early-stage cancer (OR 4.2, 95%CI 0.239-75.4; P=0.324), although these differences were not statistically significant.

Discussion

The current retrospective study evaluated bezlotoxumab as a preventive measure for rCDI in patients with cancer, a group who are at high risk for CDI and are known to have poorer outcomes and more frequent rCDI compared to the general population [14,16].

For the 177 patients who received bezlotoxumab and standard-of-care antibiotic therapy, the 90-day recurrence rate

Table 3 Univariate analysis of factors associated with rCDI after BZL treatment (N=11)

Factors	Odds ratio (95%CI)	P-value
Cancer type, hematologic vs solid cancer	0.4 (0.093-2.128)	0.310
Stage, III-IV vs. I-II	4.2 (0.239-75.4)	0.324
Number of episodes before BZL, ≥2 vs. <2[1]	0.7 (0.202-3.125)	0.748
Time from start of symptoms to BZL	0.9 (0.897-1.062)	0.571
Anti-CDI treatment[2]		
Combined antibiotic therapy vs. single therapy	1.5 (0.389-5.963)	0.545
BZL and FMT vs. no FMT	0.2 (0.049-1.383)	0.114
Length of antibiotic therapy	1.0 (0.995-1)	0.552
Hospitalization vs. no hospitalization[2]	0.217 (0.027-1.742)	0.151
Length of hospitalization[2]	1.0 (0.991-1.014)	0.606

[1]Within 80 days before BZL treatment
[2]Last BZL-related CDI/rCDI episode
rCDI, recurrent Clostridioides difficile infection; BZL, bezlotoxumab; CDI, C. difficile infection; FMT, fecal microbiota transplantation; CI, confidence interval

was 6.2%, which is notably lower than rates reported previously. Specifically, the phase III MODIFY I and II trials documented a recurrence rate of 17.8%, whereas smaller studies reported rates ranging from 10.7-16% [9,13,17-20]. Our finding of a 6.2% 90-day recurrence rate corroborates those of previous studies, highlighting bezlotoxumab's efficacy as a preventive approach in this vulnerable group.

The predisposition for rCDI in the cancer patient population arises from multiple interrelated risk factors, including immunosuppression and gut microbiota alterations, both central to the pathogenesis of CDI and its recurrence [1,2,5,8,14,21]. While the optimal strategies for preventing rCDI in patients with cancer remain unclear, non-antibiotic and nonimmune-dependent approaches, such as bezlotoxumab, could be preferable for this high-risk group [1,9]. Additionally, microbiota-targeted therapies, such as FMT, including Rebyota (live fecal microbiota) and VOWST (live fecal microbiota oral capsules), offer an effective alternative to antibiotic and immune-dependent approaches, addressing gut dysbiosis and serving as both preventive and therapeutic options in severe CDI cases [12,22-25].

Although our study did not yield statistically significant results for combined interventions, to our knowledge, it is the first to describe the use of bezlotoxumab and FMT for the prevention of rCDI within 8 weeks of last treatment. Among our 11 patients, none experienced recurrence within 90 days after the last intervention, raising the possibility of a dual treatment regimen that uses different mechanisms of action to achieve a synergistic effect. However, the literature on the efficacy of combined prophylaxis remains limited. Hoeg *et al* reported benefits of combining bezlotoxumab and FMT for high-risk patients in whom oral FMT alone did not elicit a response for rCDI, whereas Allegretti *et al* found no clear advantage of bezlotoxumab combined with FMT over FMT alone for patients with inflammatory bowel disease [26,27]. Further research is needed, but the dual strategy is promising, because bezlotoxumab acts as a toxin-binding agent while microbiota-targeted therapies restore gut microbiome balance, potentially benefiting patients who experience multiple episodes of rCDI [18,26].

The all-cause mortality rate of 47.5% in our study reflects the severity of underlying health conditions in the cancer patient population, including advanced cancer for many patients [28, 29]. Advanced-stage cancer (stages III and IV) appeared to be associated with a higher likelihood of rCDI after bezlotoxumab administration, although this observation was not statistically significant. The increased risk of rCDI in the context of advanced cancer stage may be attributed to confounding factors such as prolonged hospitalization, intensive immunosuppressive therapy and comorbidities. While our study lacked a control group to compare overall survival or mortality rates between patients receiving and not receiving bezlotoxumab, previous studies have reported no significant differences in all-cause mortality between these 2 categories of patients [17,18,30].

Because of the small sample size and the absence of a control group, our study was unable to identify significant risk factors for rCDI within this cohort. Additionally, no significant differences were observed between vancomycin- and fidaxomicin-based regimens in terms of rCDI rates or clinical remission outcomes. Both regimens demonstrated efficacy when combined with bezlotoxumab, which is consistent with findings from larger studies [5]. While fidaxomicin has been associated with a 10.8% absolute reduction in rCDI rates compared to vancomycin, its high cost and limited insurance coverage remain major barriers to its broader use [31-34]. A recent meta-analysis highlighted the cost-effectiveness of bezlotoxumab with standard-of-care antibiotics compared to standard of care alone, but did not establish a preferred cost-effective standard-of-care agent [18]. Future prospective studies may provide further insight into these associations.

Our study had several limitations that warrant cautious interpretation of the findings. The retrospective design carries inherent risks of incomplete or missing data, which may have introduced bias. Excluding patients with incomplete medication records, while reducing heterogeneity, could have introduced selection bias and further reduced our sample size. Additionally, the absence of a comparator group of patients who did not receive bezlotoxumab limits our ability to attribute observed outcomes directly to bezlotoxumab treatment. Given the relatively small sample size, we were unable to perform subgroup analyses to explore the impact of specific clinical factors. Therefore, our findings should be viewed primarily as exploratory and hypothesis-generating, underscoring the need for larger, prospective, multicenter trials to validate these results.

In this single-center, retrospective cohort study of patients with cancer who had CDI and rCDI, the 90-day rate for rCDI after treatment with bezlotoxumab was low, at 6.2%, suggesting that the benefits of bezlotoxumab are similar to those observed in the general population. These real-world findings add valuable insight into the potential role of bezlotoxumab for rCDI prevention in a high-risk oncologic setting.

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Summary Box

What is already known:

- Patients with cancer have a significantly higher risk of *Clostridioides difficile* infection (CDI) and recurrent CDI (rCDI) due to frequent antibiotic use, immunosuppression and microbiome disruption
- Bezlotoxumab, a monoclonal antibody against *C. difficile* toxin B, has demonstrated effectiveness in preventing rCDI in the general population
- Immunocompromised individuals, including those with cancer, are underrepresented in most clinical trials of bezlotoxumab
- Preventive strategies for rCDI in oncology patients remain limited and are not standardized

What the new findings are:

- This single-center, retrospective cohort study provides real-world data on bezlotoxumab use in 177 patients with cancer
- The 90-day rCDI rate after bezlotoxumab administration was low, at 6.2%, suggesting favorable outcomes
- A minority of patients received combination strategies, such as fecal microbiota transplantation, indicating potential avenues for future research
- These findings support considering bezlotoxumab as an early preventive measure in high-risk oncology patients, while underscoring the need for larger prospective studies

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