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Use of tigecycline for the management of *Clostridium difficile* colitis in oncology patients and case series of breakthrough infections

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SUMMARY

Background: *Clostridium difficile* infection (CDI) is the most frequent cause of nosocomial diarrhoea in adults. Cancer patients, in particular, are at a higher risk for CDI. Limited clinical data exist regarding the use of tigecycline for the treatment of CDI, especially in patients with oncologic and haematologic malignancies.

Aim: To characterize the use of tigecycline for treatment of CDI in oncology patients at an academic cancer centre.

Methods: This was a retrospective, single-centre, single-arm, chart review evaluating the use of tigecycline for the management of CDI in oncology patients at an academic cancer centre.

Findings: The median age of CDI diagnosis in this patient group ($N = 66$) was 65 years (range: 16–84) and the majority of patients had solid tumour malignancies. Fifty-six percent of patients had severe CDI, 70.3% of which were classified as having severe complicated disease. The median time to initiation of tigecycline therapy was 2 days (mean: 3.83) and the median number of tigecycline doses was 13 (range: 1–50). Twelve non-CDI breakthrough infections were observed, and four patients developed CDI while receiving tigecycline for non-CDI indications. The rate of death was 18% and the recurrence rate was 15.2%.

Conclusion: Tigecycline did not lead to overt benefits in outcomes of oncology patients with CDI when compared to historical data. In addition, several breakthrough CDIs were observed in patients who received the drug for a non-CDI indication. Further prospective research is needed to validate the use of tigecycline for management of CDI.

Introduction

Clostridium difficile infection (CDI) is the most frequent cause of nosocomial diarrhoea in adults.[1] The clinical manifestations of CDI range from mild diarrhoea to fulminant colitis and severe sepsis, which may be life-threatening.[2,3] Whereas metronidazole and oral vancomycin have been

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effective treatment modalities for CDI for several decades, the emerging resistance patterns and increasing rates of recurrent and refractory disease have created a need for novel therapies.[4] Cancer patients, in particular, are at a higher risk for CDI, with six- and nine-fold higher rates in oncology and haematopoietic stem cell transplant patients, respectively, compared to non-cancer patients.[5,6] Reasons for this observation include a depressed immune response, prolonged hospitalization, exposure to chemotherapy and proton-pump inhibitors, and repeated antibiotic treatments with fluoroquinolone prophylaxis and broad-spectrum agents.[7]

Fidaxomicin, a macrocyclic oral antibiotic, was the first agent approved in more than two decades by the US Food and Drug Administration (FDA) for the management of CDI.[8] Although approved in 2011, this agent has not been studied in patients with severe complicated CDI. Besides intravenous metronidazole and rectal vancomycin, the above-mentioned agents are primarily administered orally and this may become problematic in patients who are unable to tolerate oral therapies, such as those who are critically ill, or those with ileus. This may also be applicable to oncology-specific scenarios such as patients with severe chemotherapy-induced mucositis or graft-versus-host disease of the gastrointestinal tract.

Tigecycline is a broad-spectrum intravenous glycylcycline antibiotic that is approved by the FDA for the treatment of community-acquired pneumonia, complicated skin and soft tissue infections, and intra-abdominal infections.[9] This agent has also been utilized for the management of liver abscesses, spontaneous bacterial peritonitis, secondary peritonitis, as well as multidrug-resistant Gram-negative rod infections and non-tuberculosis mycobacterial infections. In addition, several in-vitro studies have demonstrated activity of tigecycline against *C. difficile* isolates.[10–13] Based on achieved faecal concentrations, the drug appears to surpass minimum inhibitory concentrations among multidrug-resistant strains of *C. difficile* in comparison to its achieved faecal concentrations at standard doses.

The majority of published data pertaining to the use of tigecycline for the management of CDI are descriptive and/or retrospective in nature. Conversely, in-vivo animal studies appear to demonstrate negative results. A study conducted in murine models treated with tigecycline demonstrated alteration in the gastrointestinal microbiota that led to increased susceptibility to CDI.[5] A case series published by Britt *et al.* examined seven cases of severe and complicated CDI and found that the addition of tigecycline led to a clinical cure in six of the seven patients who were being treated with vancomycin and metronidazole with a sustained response at 28 days.[14] However, a study published by Thomas *et al.* in 2014 that compared outcomes in severe CDI in 18 patients who received tigecycline versus those who did not found no difference in terms of survival or need for colectomy.[15]

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) group published an update of the treatment guidance document for CDI in 2014.[16] The guidelines cited the use of tigecycline in their recommendations, but only for severe disease and/or complicated or refractory CDI as salvage therapy for 14 days when oral therapy is not possible. The recommendation for this approach carried a 'C' strength of recommendation as well as a level III quality of evidence grade.

Limited clinical data exist regarding the use of tigecycline for the treatment of CDI, especially in patients with oncologic and haematologic malignancies. Therefore, the objective of this study is to characterize the use of tigecycline for the management of CDI in oncology patients at our academic cancer centre.

Methods

A retrospective review was conducted of oncology patients who received intravenous tigecycline for the management of CDI between July 2008 and October 2015 at a National Cancer Institute (NCI)-designated academic cancer centre. This study was approved by both the Moffitt Cancer Center Scientific Review Committee and the University of South Florida Institutional Review Board. The patient list was generated from the Laboratory Information Management System (LIMS) database. Electronic medical records were screened to obtain detailed information on patient demographics, disease characteristics, CDI diagnostic assays, and treatment-related factors.

All patients diagnosed with *C. difficile* colitis and treated with tigecycline were included in our assessment. Patients were excluded if they received tigecycline for a non-CDI indication. The primary objective was to determine the proportion of patients treated with tigecycline for management of CDI that met the current guideline definition for severe and severe complicated *C. difficile* colitis, as well as refractory *C. difficile* colitis.[1,17] Secondary objectives included time to tigecycline initiation after CDI diagnosis, incidence of nausea and vomiting after tigecycline initiation, transfer to intensive care unit, use of intravenous immunoglobulin, use of acid suppressants, surgery, frequency of CDI relapse, and incidence of breakthrough infections while on tigecycline therapy.

CDI was defined as presence of diarrhoea and a stool sample positive for *C. difficile* toxin immunoassay or polymerase chain reaction.[1] Severe infection was defined as CDI with one or more of the following attributed to the infection: white blood cell count $\geq$15,000 cells/μL; serum creatinine $\geq$1.5 times baseline.[1] Patients who were neutropenic (absolute neutrophil count $<$500 cells/μL) at diagnosis of CDI were considered to have severe disease if the serum creatinine was $>$50% baseline. Severe complicated CDI was defined as above plus one or more of the following attributable to CDI: hypotension (systolic blood pressure $<$90 mmHg and/or diastolic blood pressure $<$60 mmHg), ileus, toxic megacolon or colitis on computed tomography or X-ray, perforation, need for colectomy, or intensive care unit admission for severe disease.[1,16] Patients were considered to have refractory CDI if they received more than three days of metronidazole, vancomycin, or both without improvement.[17] Relapsed CDI was defined as a new diagnosis of CDI at least three months after completion of appropriate therapy for the initial CDI episode.

Results

A total of 105 oncology patients received tigecycline during the study period. Of the 105 cases identified, 66 patients received the agent for the management of CDI. Baseline characteristics are displayed in Table I. Within the study group, the median age was 65 years (range: 16–84), and half of these patients were elderly (age $>$65 years). A wide variety of malignancy types were seen, the majority being solid tumour in