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Clostridium difficile-associated diarrhoea, a frequent complication in patients with acute myeloid leukaemia

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Abstract Diarrhoea occurs frequently in neutropenic patients with acute leukaemia receiving chemotherapy and may be caused by either infection- or drug-induced cytotoxicity. Since *Clostridium difficile* is the most common cause of nosocomial infectious diarrhoea in non-haematologic patients, we were interested in its incidence in patients with acute myeloid leukaemia (AML). In this retrospective study, we analysed 134 patients with AML receiving a total of 301 chemotherapy courses. Diarrhoea occurred during 33% of all courses in 58 patients. *C. difficile*-associated diarrhoea (CDAD) occurred in 18% of all patients and 9% of all treatment courses. Almost one third of diarrhoea episodes were caused by *C. difficile*. CDAD was associated with older age (58 vs. 50 years), number of antibiotics administered (2 vs. 1), duration of antibiotic therapy (7 vs. 4 days), ceftazidime as the antibiotic of choice (75% vs. 54%) and duration of neutropenia (12 vs. 7 days) prior to onset of diarrhoea. An increased risk for CDAD was seen for prolonged neutropenia. CDAD responded well to oral metronidazole and/or vancomycin

and no patient died of this complication. In conclusion, CDAD is common in patients with AML receiving chemotherapy. *C. difficile* enterotoxin testing of stool specimens should be included in all symptomatic patients.

Keywords *Clostridium difficile* · Diarrhoea · Enterocolitis · Acute myeloid leukaemia · Neutropenia

Introduction

Patients with acute myeloid leukaemia (AML) have severe neutropenia, either due to the leukaemic burden or the cytotoxic effects of chemotherapy, which usually consists in a combination of cytarabine (Ara-C) and an anthracycline such as idarubicine or daunorubicine [1, 2] rendering patients susceptible to life-threatening infections and/or mucositis. Since infections are a major cause for morbidity and mortality in patients with acute leukaemia, institution of empirical antibiotic therapy is mandatory if fever occurs in neutropenic patients [3]. The use of antibiotic prophylaxis is still common in many centres. However, antibiotic use is an important risk factor for *Clostridium difficile*-associated diarrhoea (CDAD), since antibacterial drugs suppress resident bowel flora and thus permit overgrowth of *C. difficile* [4–7]. Enteric infections with other pathogens are also common in patients with acute leukaemia [8]. Neutropenic enterocolitis is a severe complication of aggressive chemotherapy in these patients and occurs in about 6% [8, 9] with *C. difficile* often being the underlying pathogen [10]. However, diarrhoea may be caused by abdominal infection, intestinal mucositis or other toxic effects of chemotherapy [8]. On the other hand, cytotoxic chemotherapy, such as Ara-C, may also induce *C. difficile* colitis [11, 12].

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Thus, CDAD is a common complication in patients with haematological malignancies after myelosuppressive chemotherapy [13]. Since we observed an increase in the incidence of diarrhoea in patients with AML, we decided to initiate this retrospective study. The aim of this study was to evaluate clinical data and risk factors for patients with AML developing CDAD after aggressive chemotherapy.

Materials and methods

All medical records of patients diagnosed with AML at our hospital between January 2003 and March 2008 were reviewed retrospectively. Only patients receiving Ara-C/anthracycline-based chemotherapy (e.g. Ara-C/idarubicine “3+7”) were included in this analysis. Patients receiving low-dose Ara-C s.c. or oral chemotherapy were excluded from this study.

In all patients with diarrhoea, stool samples for *C. difficile* enterotoxin and cytotoxin detection (toxin A and B; RIDASCREEN®, R-Biopharm, Darmstadt, Germany) had been obtained. This enzyme-linked immunosorbent assay has a sensitivity and a specificity of 91.7% and 100.0%, respectively (manufacturer’s information). Furthermore, stool samples were cultured for *Salmonella*, *Shigella*, *Yersinia enterocolitica* and *Campylobacter coli/jejuni* using standard culture techniques.

Neutropenia was defined as absolute neutrophil count $<1.0 \times 10^9/L$. CDAD was defined as diarrhoea (≥ 3 unformed stools per 24 h) in the presence of a positive *C. difficile* toxin test. Diarrhoea due to other causes than *C. difficile* was termed non-CDAD. Severe enterocolitis due to *C. difficile* was diagnosed if bloody diarrhoea, fever (axillary temperature $\geq 38.3^\circ C$) and abdominal pain occurred.

Clinical response was defined as resolution of diarrhoea within 12 days of appropriate therapy without deterioration of other abdominal symptoms. Treatment failure was defined as deterioration of abdominal symptoms, persistence of diarrhoea after 12 days of appropriate therapy or progression to severe enterocolitis. Recurrence was defined as a new episode of diarrhoea with detection of *C. difficile* toxin during the subsequent chemotherapy course.

Antibiotic prophylaxis during neutropenia had not been used according to our institution’s policy. Patients with febrile neutropenia received ceftazidime (2,000 mg t.i.d. i.v.) as first-line treatment according to our institutional guidelines. Student’s *t* test, Fisher’s exact test, odds ratio (OR) with the 95% confidence interval (95%CI) and Pearson’s correlation coefficient (*R* value) were used for statistical analyses. Two-sided *P* values <0.05 were considered as statistically significant.

Results

General findings

In this study, 134 consecutive patients with AML receiving Ara-C-based chemotherapy were included. Mean age was 53 years (range 18–75 years), whereas 43% of the patients were ≥ 60 years old. The male/female ratio was equally balanced. Approximately two thirds of the patients (87 out of 134) had de novo AML. A total of 301 chemotherapy courses was administered (mean 2, range 1–5). The majority of all patients received Ara-C doses $\geq 6,000$ mg/m² per chemotherapy course (67.1%, 202 out of 301). In six courses (2.0%) no Ara-C was administered, i.e. idarubicine alone or busulfan/cyclophosphamide was given. Diarrhoea occurred in 40.6% of patients. Twenty-eight episodes of CDAD occurred in 24 patients with an overall incidence of CDAD of 17.9% per patient with AML.

Diarrhoea of any cause occurred in 100 chemotherapy courses (33.2%) in 58 patients with a mean duration of 6 days (range 1–31 days). In 28 diarrhoea episodes (28.0%), *C. difficile* was found. Thus, CDAD occurred in 28 of 301 (9.3%) chemotherapy courses (Table 1). CDAD occurred during the first chemotherapy course in 44.0% of patients, followed by the second (24.0%), the third (12.0%), the fourth (12.0%) and the fifth (8.0%). Three patients had two episodes of CDAD in consecutive chemotherapy courses. Only one patient developed CDAD without prior antibiotic treatment. *Salmonella*, *Shigella*, *Y. enterocolitica*, and *C. coli/jejuni* were not found in any stool samples of AML patients with diarrhoea.

Table 1 Clinical characteristics of patients

Clinical characteristic	Value
Patients	
<i>n</i>	134
Age, years (range)	53 (18–75)
Sex, male/female	1:1
AML, <i>n</i> (%)	
De novo	87 (64.9)
Secondary	30 (22.4)
Relapsed	17 (12.7)
Chemotherapy courses	
Administered, <i>n</i> (mean, range)	301 (2, 1–5)
Ara-C dose $\geq 6,000$ mg/m ² per course, <i>n</i> (%)	202 (67.1)
Episodes of diarrhoea	
<i>n</i>	100
Duration, days (range)	6 (1–31)
Caused by <i>C. difficile</i> , <i>n</i> (%)	28 (28.0)

Ara-C cytarabine

Clinical features of patients with CDAD

In the comparison of the clinical features of AML patients with CDAD ($n=28$) and non-CDAD ($n=72$), we found age (58 vs. 50 years, $P=0.02$), number of antibiotics administered (2 vs. 1, $P=0.03$), use of ceftazidime (75.0% vs. 54.2%, $P=0.046$), duration of antibiotic use (7 vs. 4 days, $P=0.01$) and duration of neutropenia (12 vs. 7 days, $P=0.01$) prior to onset of diarrhoea to be associated with a higher risk for CDAD. However, duration of diarrhoea (8 vs. 6 days, $P=0.25$) and administered Ara-C dose (5,336 vs. 5,774 mg/m² per course, $P=0.66$) were not associated with a higher risk for CDAD (Table 2).

In patients with CDAD, more than one half (57.1%, 16 out of 28) had neutropenia ≥ 10 days, but only one third (24 out of 72) of patients with non-CDAD had prolonged neutropenia prior to onset of diarrhoea.

In univariate analysis, duration of neutropenia ≥ 10 days prior to onset of diarrhoea only was associated with an increased risk for CDAD (OR=2.7 [95%CI=1.09–6.52]). However, there was no significantly higher risk for older patients (age ≥ 60 years) (OR=1.7 [95%CI=0.67–4.14]), antibiotic therapy per se (OR=2.6 [95%CI=0.82–8.52]), duration of antibiotic therapy ≥ 10 days (OR=1.7 [95%CI=0.58–4.79]) prior to onset of diarrhoea and Ara-C dose $\geq 6,000$ mg/m² per course (OR=0.5 [95%CI=0.21–1.24]). A trend was seen for ceftazidime therapy (OR=2.5 [95%CI=0.96–6.72]) prior to onset of diarrhoea. In contrast, correlation of risk factors with the development of CDAD is very low (Table 3).

Treatment and outcome of CDAD

In 92.9% (26 out of 28) of all CDAD episodes, patients were treated with either metronidazole 400 mg t.i.d. p.o. or vancomycin 250 mg q.i.d. p.o. In two episodes, patients received no antibiotic therapy because diarrhoea had already stopped spontaneously when the test results arrived. All four episodes of recurrent CDAD occurred in two consecutive chemotherapy courses. In three cases, metronidazole, and in one case, vancomycin was administered as primary therapy. One patient received metronidazole due to

soft tissue infection prior to CDAD wherefore primary vancomycin therapy of CDAD was started. Treatment failure of primary metronidazole therapy was seen in three cases, but not of primary vancomycin therapy (Table 4). Severe enterocolitis developed in 17.9% (five out of 28) of all CDAD episodes. Of these, 80.0% (four out of five) were treated initially with metronidazole and one with vancomycin. No patient died of CDAD.

Discussion

In our retrospective single-centre study, we found that diarrhoea is a common complication among AML patients receiving chemotherapy. Diarrhoea occurred in about 40% of patients and in one third of all chemotherapy courses. *C. difficile* was the causative agent in approximately one third of all diarrhoea episodes and thus it is a major contributor to this complication. Interestingly, stool cultures revealed no other bacterial infectious agents such as *Salmonella*, *Shigella*, *Yersinia* or *Campylobacter* in any diarrhoea episode, which is an important finding, showing that diarrhoea in leukaemia patients, although a common complication, is caused rather by factors associated with the underlying disease itself or therapy complications rather than the lack of hygiene in the hospital setting.

Diarrhoea is a common adverse event in patients with acute leukaemia [8]. In AML patients treated with Ara-C, diarrhoea was seen in up to 100% in a previous study [14] and partly depended on total dose and duration of treatment [15]. Fatal infectious complications have been dreaded in patients with acute leukaemia [16]. Neutropenic enterocolitis-related death rate is with about 30% very high in these patients. Risk factors for diarrhoea and enterocolitis, respectively, are neutropenia, infections, and drug-induced alterations of the bowel mucosal surface [9].

The incidence of CDAD in patients with AML is 18% per patient and 9% per chemotherapy course. In a heterogeneous patient group with AML, acute lymphoblastic leukaemia, chronic myeloid leukaemia in blast crises, and aggressive non-Hodgkin lymphoma, the incidence of CDAD was 5–7% per chemotherapy course [8, 13].

Table 2 Comparison of clinical features of patients with diarrhoea

Clinical feature	CDAD ($n=28$)	Non-CDAD ($n=72$)	<i>P</i> value
Age, years (range)	58 (22–75)	50 (18–70)	0.02
Duration of diarrhoea, days (range)	8 (2–31)	6 (1–31)	0.25
Number of antibiotics ^a , <i>n</i> (range)	2 (0–5)	1 (0–3)	0.03
Ceftazidime therapy ^a , <i>n</i> (%)	21 (75.0)	39 (54.2)	0.046
Duration of antibiotic therapy ^a , days (range)	7 (0–21)	4 (0–17)	0.01
Duration of neutropenia ^a , days (range)	12 (0–33)	7 (0–22)	0.01
Ara-C dose, mg/m ² per course (range)	5,336 (0–18,000)	5,774 (0–10,000)	0.66

^a Prior to onset of diarrhoea

Table 3 Risk factors for developing CDAD

Clinical feature	OR [95%CI]	R value	P value
Age \geq 60 years	1.7 [0.67–4.14]	0.14	0.35
Antibiotic therapy per se ^a	2.6 [0.82–8.52]	0.15	0.13
Antibiotic therapy \geq 10 days ^a	1.7 [0.58–4.79]	0.08	0.40
Ceftazidime therapy ^a	2.5 [0.96–6.72]	0.19	0.07
Neutropenia \geq 10 days ^a	2.7 [1.09–6.52]	0.22	0.04
Ara-C dose \geq 6,000 mg/m ² per course	0.5 [0.21–1.24]	-0.15	0.16

Ara-C cytarabine

^a Prior to onset of diarrhoea

Interestingly, CDAD occurred in about two thirds of the cases in the first two therapy courses. Perhaps, it is due to the leukaemic tumour burden of the bowel. In most cases, thickening of the bowel wall is not caused by mucositis but by infections. In very rare cases, thickenings are caused by leukaemic infiltration of the bowel [8]. Recently, leukaemia was identified to be a significant independent risk factor for CDAD [17].

In an in vitro study, it could be shown that Ara-C has no cytotoxic activity against *C. difficile*. In patients with leukaemia, Ara-C use represents a risk factor altering the intestinal flora and so lowering the colonisation resistance, which leads to *C. difficile* overgrowth if antibiotics are used [18]. Interestingly, a higher Ara-C dose seems to be protective for CDAD as OR=0.5. Similar results were found by Gorschlüter et al. [8]: The incidence of diarrhoea in patients who had received high-dose Ara-C was significantly lower compared with patients who were treated with standard-dose Ara-C. This observation is in contrast with reports in which the mucosal-damaging effects of high-dose Ara-C have been implicated in the pathogenesis of invasive bacterial and fungal infections [8].

Antibiotic therapy per se (OR=21.3), especially cephalosporin therapy (OR=2.6), is associated with significantly increased risk for CDAD [19]. In a recent study of antibiotic use and subsequent CDAD in hospitalised patients, ceftazidime was shown to be associated with a significantly increased risk (OR=1.8) of acquiring CDAD [20]. This is in accordance with our findings in patients with AML (OR=2.5).

Table 4 Response to therapy among patients with CDAD (n=28)

Treatment	n (%)
Metronidazole	19 (73.1)
Response	16 (84.2)
Treatment failure	3 (15.8)
Recurrence	3 (15.8)
Vancomycin	7 (26.9)
Response	7 (100.0)
Treatment failure	0
Recurrence	1 (14.3)

AML is a disease of older adults with a median age at diagnosis of 67 years [21]. In this study, CDAD was more frequent in older patients. Age as an accepted risk for developing CDAD [6, 19] may be due to the higher comorbidity rate in the elderly.

The risk of superinfection with *C. difficile* in patients with haematological malignancies and antimicrobial treatment appears to increase with the grade and duration of neutropenia [22]. In our study, we could show that neutropenia is a risk factor for developing CDAD (OR=2.7). About 85% of patients with acute leukaemia undergoing aggressive chemotherapy develop infections and/or fever during the neutropenic phase [3]. So, perhaps, the higher CDAD rate for neutropenic patients is due to the more frequent use of antibiotic agents, since it has been shown that antibiotic use is associated with CDAD. The incidence of CDAD is 7% per patient after autologous peripheral blood stem cell transplantation (SCT), slightly lower than in acute leukaemia [23]. In a cohort of patients receiving an allogenic or autologous haematopoietic SCT, the incidence of CDAD was 14% per patient [24]. The lower incidence of CDAD in patients with autologous peripheral SCT may reflect the duration of neutropenia in this setting (7 days) [23] in comparison to both allogenic or autologous SCT (14 days) [25] or conventional AML therapy (21 days) [26]. More than one half (58%) of *C. difficile* infections occurred in patients with neutropenia in comparison to the non-neutropenic phase after haematopoietic SCT [25].

Classic bacterial enteric pathogens in patients with acute leukaemia- and chemotherapy-related neutropenia have a low incidence of about 1% [8, 27]. Also, we found no enteric infection by other enteropathogenic bacteria and gram-negative sepsis, respectively. In 18% of CDAD episodes, patients developed severe enterocolitis. This was more frequently seen, as reported by Gorschlüter et al. to be 8% [13]. Fortunately, no patient died due to CDAD.

CDAD is a major concern for health care systems and clinicians [28]. Morbidity and mortality from CDAD increased in recent years [29–31], which might also have an impact on leukaemia patients. Unfortunately, clear data of increasing incidence of CDAD for patients with

haematological malignancies are not available so far. Recent outbreaks of CDAD with increased severity, high relapse rate and significant mortality have been related to the emergence of a new, hypervirulent *C. difficile* strain worldwide. The emerging strain is referred to as NAP1 and PCR ribotype 027 [31, 32]. In our series, we have not tested for hypervirulent *C. difficile* strains.

Current diagnosis of CDAD is based on methods that specifically detect toxin A and/or toxin B in stool samples or detect both toxigenic and non-toxigenic strains of *C. difficile* (e.g. by culture on selective media or detection of a *C. difficile* surrogate marker antigen in stool specimens) [5, 33]. Sensitivity and specificity of enzyme immunoassays for detection of *C. difficile* toxins A and B are 91% (range 88–93%) and 100%, respectively. These tests are valuable methods for the diagnosis of CDAD [33]. Since the sensitivity of our used toxin test is 92%, only 8% of patients with diarrhoea escape the diagnosis of CDAD. The rate of false-negative tests could be reduced by repetitive toxin tests within 7 days (with the highest detection rate on days 3–4) [34].

Metronidazole has been recommended as initial therapy since the late 1990s and continues to be the first choice for all but seriously ill patients and those with complicated or fulminant infections or multiple recurrences of CDAD for whom vancomycin is recommended [35]. Metronidazole should be particularly preferred due to the emergence of vancomycin-resistant enterococci (VRE) [36, 37]. *C. difficile* infection is a risk factor for bacteraemia due to VRE in VRE-colonised patients with acute leukaemia [38]. After the emergence of hypervirulent *C. difficile* strains in 2003, vancomycin was no longer superior to metronidazole in avoiding complications of CDAD [39]. The mean response rate to metronidazole is 86% (range 74–95%). The low rate of 74% is associated with an epidemic *C. difficile* strain [35, 39]. For sick patients, such as AML patients, empirical therapy should be started as soon as CDAD is suspected [31]. In our study, the response rate to metronidazole p.o. was 84%, slightly lower than the 91% reported by Gorschlüter et al. [13]. Vancomycin p.o. is effective in metronidazole failure as the response rate was 100%.

In conclusion, diarrhoea is common in patients with AML undergoing Ara-C-based chemotherapy and CDAD accounts for one third of all episodes. Therefore, stool specimens should be tested for *C. difficile* thus prompt therapy can be initiated.

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