Clinically defined chemotherapy-associated bowel syndrome predicts severe complications and death in cancer patients

Maria J.G.T. Vehreschild,[1] Arne M.K. Meißner,[1] Oliver Andreas Cornely,[2] Georg Maschmeyer,[3] Silke Neumann,[4] Marie von Lilienfeld-Toal,[5] Meinholf Karthaus,[6] Mohammed Wattad,[7] Peter Staib,[8] Martin Hellmich,[9] Hildegard Christ,[9] and Jörg Janne Vehreschild[1]

[1]1st Department of Internal Medicine, University of Cologne, Cologne; [2]1st Department of Internal Medicine, University of Cologne, Cologne; Clinical Trials Centre Cologne, ZKS Köln (BMBF 01KN0706), University of Cologne, Cologne; Center for Integrated Oncology COI KölnBonn, University of Cologne, Cologne; Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases CECAD, University of Cologne, Cologne; [3]Department of Hematology, Oncology and Palliative Care, Ernst-von-Bergmann Klinikum, Potsdam; [4]Department of Hematology and Oncology, Georg-August-University Göttingen, Göttingen; [5]3rd Department of Internal Medicine, University Hospital Bonn, Bonn; [6]Department of Hematology and Oncology, Klinikum Neuperlach, Munich; [7]Department of Hematology/Oncology/Stem-Cell-Transplantation, Kliniken-Essen-Süd, Essen; [8]Department of Hematology/Oncology, St. Antonius Hospital, Eschweiler, and [9]Department of Medical Statistics, Informatics and Epidemiology, University of Cologne, Cologne, Germany

Funding: this study was supported by the Deutsche Forschungsgemeinschaft (German Research Foundation), DFG RU-15781-1. OAC is supported by the German Federal Ministry of Research and Education (BMBF grant 01KN0706).

Manuscript received on June 16, 2011. Revised version arrived on July 18, 2011. Manuscript accepted on August 16, 2011.

Correspondence:
Maria J.G.T. Vehreschild, Hospital of the University of Cologne, Kerpener Straße 62, 50937 Köln Germany.
Phone: international +49.022.14786494.
Fax international +49.021.4783611.
E-mail: maria.vehreschild@ctuc.de

ABSTRACT

Background
Neutropenic patients are at risk of abdominal complications and yet the incidence and impact of these complications on patients' morbidity and mortality have not been sufficiently evaluated. We aimed to assess a clinical rule for early detection of abdominal complications leading to death or transfer to intensive care in patients with chemotherapy-associated neutropenia.

Design and Methods
This observational multicenter study was carried out in seven German hematology-oncology departments. For inclusion, neutropenia of at least 5 consecutive days was required. Risk factors for "transfer to intensive care" and "death" were assessed by backward-stepwise binary logistic regression analyses. Chemotherapy-associated bowel syndrome was defined as a combination of fever (T ≥37.8 °C) and abdominal pain and/or lack of bowel movement for 72 hours or more. Five hundred and twenty-one neutropenic episodes were documented in 359 patients.

Results
The incidence of chemotherapy-associated bowel syndrome was 126/359 (35%) in first episodes of neutropenia. Transfer to intensive care occurred in 41/359 (11%) and death occurred in 17/359 (5%) first episodes. Chemotherapy-associated bowel syndrome and duration of neutropenia were identified as risk factors for transfer to intensive care (P<0.001; OR 4.753; 95% CI 2.297-9.833, and P=0.003; OR 1.061/d; 95% CI 1.021-1.103). Chemotherapy-associated bowel syndrome and mitoxantrone administration were identified as risk factors for death (P=0.005; OR 4.611; 95% CI 1.573-13.515 and P=0.026; OR 3.628; 95% CI 1.169-11.256).

Conclusions
The occurrence of chemotherapy-associated bowel syndrome has a significant impact on patients' outcome. In future interventional clinical trials, this definition might be used as a selection criterion for early treatment of patients at risk of severe complications.

Key words: neutropenia, chemotherapy-associated bowel syndrome, risk prediction.

Citation: Vehreschild MJGT, Meißner AMK, Cornely OA, Maschmeyer G, Neumann S, von Lilienfeld-Toal M, Karthaus M, Wattad M, Staib P, Hellmich M, Christ H, and Vehreschild J-J. Clinically defined chemotherapy-associated bowel syndrome predicts severe complications and death in cancer patients. Haematologica 2011;96(12):1855-1860. doi:10.3324/haematol.2011.049627

Introduction

Empirical antimicrobial treatment has been recognized as an efficient means to reduce the morbidity and mortality of neutropenic patients with cancer. Major guidelines offer detailed treatment strategies for the management of fever or pulmonary infiltrates during neutropenia.[1-3] While abdominal complications are common in neutropenic patients, they have not been studied to a similar extent, leaving treating physicians at a loss for effective treatment strategies. A review of the literature reveals that diarrhea and neutropenic enterocolitis are the two major clinical complications in this field.[4-11]

Where specified, definitions of diarrhea vary only slightly across trials, usually requiring at least three or four unformed stools within 24 h.[4-12] *Clostridium difficile (C. difficile)* has frequently been identified as the causative pathogen, with reported incidence rates ranging from 4.8-9% in patients with acute myelogenous leukemia, from 4.9-7.5% in patients undergoing autologous stem cell transplantation and from 14-30.4% in those undergoing allogeneic stem cell transplantation.[5,6,9,11,13,14] Other associated factors include prior use of antibiotics or certain antineoplastic agents, e.g. fluoropyrimidines, irinotecan hydrochloride, methotrexate or cisplatin.[4,15-17]

The pathogenesis of neutropenic enterocolitis is regarded as a multifactorial process. After administration of cytotoxic agents damage to the mucosal barrier is exacerbated by bacterial, fungal and/or viral invasion. In patients with impaired host defenses, these pathogens may cause blood stream infections after penetrating bowel wall.[12,18] Neutropenic enterocolitis has been associated with mortality rates of 50% and higher.[9,12,19,20] Incidence rates between 3.5 and 28% have been reported.[4,12,21] In a meta-analysis, a pooled incidence rate of 5.3% was calculated for patients with hematologic malignancies or receiving high-dose chemotherapy for solid tumors or aplastic anemia.[10] All trials included were limited by their small size, retrospective design and/or varying case definitions.

Heterogeneity among the definitions of neutropenic enterocolitis is a particular matter of concern.[4,7,9,10] Most authors agree that fever, abdominal symptoms, e.g. pain, tenderness and diarrhea, as well as demonstration of bowel wall thickening in imaging studies should be part of the definition. While such a definition can be useful to describe the full-blown picture of neutropenic enterocolitis, any intervention at this stage holds little promise with respect to the patients' outcome. Furthermore, little is known about the outcome of patients who do present with abdominal symptoms but do not fulfill the above mentioned criteria for neutropenic enterocolitis. For example, a patient may present with fever and ileus, but without bowel wall thickening. The current basis of evidence does not allow any predictions with respect to a patient's prognosis. Neutropenic enterocolitis might be one possible result of chemotherapy-associated impairment of intestinal function; however, other clinical constellations might be just as relevant.

In conclusion, the authors believe that patients at risk of clinical deterioration due to abdominal complications should be identified at the earliest stage possible. The authors hypothesize that changes in bowel habits or abdominal pain associated with fever and neutropenia are the lowest common denominator of all chemotherapy-associated abdominal conditions. In this context, the present study evaluates a clinical rule for early detection of abdominal complications that might lead to death or transfer to intensive care in patients with chemotherapy-associated neutropenia.

Design and Methods

Study design

The present study was carried out as a multicenter observational study at seven German hematology-oncology departments from June 2009 to May 2010. All centers were using the CoDan (Cologne Nursing Standard for the Documentation of Diarrhea and Abdominal Complaints during Neutropenia) – a daily self-assessment distributed to all patients after administration of chemotherapy until the end of neutropenia – as a standard of care. Assessment included abdominal pain (yes/no), frequency of overall stools, number of formed stools, number of unformed stools, green coloration of feces (yes/no) and melena (yes/no). All patients were regularly offered assistance in filling in the CoDan. For patients unwilling or unable to fill in the CoDan, study documentation was based on the patients' records.

Patients recovering from neutropenia were screened by a study assistant (site personnel) with respect to inclusion and exclusion criteria. Inclusion criteria were an absolute neutrophil count of less than 500 neutrophils/μL or a white blood count below 1,000 leukocytes/μL for at least 5 consecutive days. Exclusion criteria comprised prior diagnosis of an inflammatory bowel disease such as ulcerative colitis or Crohn's disease, presence of diarrhea (predefined as ≥3 unformed stools per day or >200 mL loose stool in patients with a rectal stool collector) or abdominal pain during or prior to administration of chemotherapy and use of prophylactic intravenous or oral metronidazole or oral vancomycin. All study assistants had been personally trained by the study coordinator (MV) before initiation of screening.

The study was approved by the ethics committee of the University of Cologne, Germany (#09-094). Being a non-interventional observational trial engaging only site-personnel involved in the care of the patients for documentation of anonymized data, no informed consent was needed for inclusion in the analysis. The study was registered at the German Clinical Trials Register (ID: DRKS00000111).[22]

Documentation

Data from eligible patients were anonymized and entered into web-based electronic case report forms.[23] The information collected included: year of birth, gender, weight, height, underlying disease requiring chemotherapy, current chemotherapy regimen, administration of laxatives, proton pump inhibitors, H2 receptor blockers, anti-infective agents, duration of current neutropenic episode, frequency of formed and unformed stools, presence of abdominal pain, presence of fever (T ≥37.8°C), duration of stay in an intensive care unit, partial or total colectomy, death, and death attributable to abdominal complications. The design of the database enabled documentation of these items on a day-to-day basis.

In the event of (i) diarrhea, defined as three or more unformed stools per day or more than 200 mL of loose stool in patients with a fecal collector, or (ii) chemotherapy-associated bowel syndrome (CABS), defined as a combination of fever (T ≥37.8 °C) and abdominal pain and/or lack of bowel movement for at least 72 h, the documentation was extended to include the following items: pathological findings on abdominal ultrasound, X-rays, magnetic resonance imaging and computed tomography scans, results of stool and blood cultures, and C-reactive protein and procalcitonin values. The documentation for each episode started

with the first day of chemotherapy and ended with the last day of neutropenia or death, whichever occurred first.

Statistical analysis

All statistical analyses were carried out using SPSS software (SPSS, version 18.0.2, Somer, NY, USA). Incidence rates were calculated. To assess potential risk factors for the occurrence of CABS, a backward-stepwise binary logistic regression analysis was performed. Variables were pre-defined based on a literature search on potential risk factors for abdominal complications: administration of antibiotics, duration of neutropenia and underlying disease (acute myeloid leukemia, myelodysplastic syndrome, acute lymphoblastic leukemia, solid tumor, multiple myeloma). Chemotherapeutic agents were included as follows: high dose nitrogen mustard alkylating agents (cyclophosphamide >50 mg/kg, ifosfamide >10,000 mg/m^2 or melphalan >200 mg/m^2), low dose nitrogen mustard alkylating agents (cyclophosphamide ≤50 mg/kg, ifosfamide ≤10000 mg/m^2 or melphalan ≤200 mg/m^2), steroids, topoisomerase inhibitors, anthracyclines, high-dose cytarabine (>3 g/m^2), other pyrimidine analogues, high-dose methotrexate (>1000 mg/m^2), and mitoxantrone.

To assess potential risk factors for the endpoints "transfer to intensive care" and "death", another literature search was carried out to pre-define a set of variables: age, occurrence of fever, duration of neutropenia, occurrence of diarrhea, occurrence of CABS and underlying disease (acute myeloid leukemia, myelodysplastic syndrome, or acute lymphoblastic leukemia). Chemotherapeutic agents were included as follows: anthracyclines, high dose cytarabine (>3 g/m^2), mitoxantrone. Using these variables a second backward-stepwise binary logistic regression analysis was performed.

The t-test for dependent samples was used to compare maximum C-reactive protein values within 3 days prior to and after the diagnosis of CABS.

For all analyses, a P value less than 0.05 was considered statistically significant.

Results

Study population and outcomes

The study progress is shown in Figure 1. At the end of the study period, 1,622 neutropenic episodes in 1,071 patients had been screened: 526 episodes in 362 patients fulfilled the study inclusion criteria. Five files could not be found, so 521 episodes in 359 patients were entered into the study. At least one consecutive episode was documented for 105 patients (29%).

Of the 359 patients, 208 (58%) were male. The median age was 56 years (range, 18 - 83), the median weight 75 kg (range, 38 - 154), and the median height 172 cm (range, 147-204). The median duration of first episodes of neutropenia was 9 days (range, 5-47). Indications for chemotherapy and chemotherapeutic agents administered during first episodes of neutropenia are shown in Table 1.

The overall incidence of diarrhea was 160/359 (45%) in first episodes of neutropenia and 206/521 (40%) in all episodes, while the incidence of CABS was 126/359 (35%) in first episodes and 161/521 (31%) in all episodes. Out of the 105 patients with a documented second neutropenic episode, 21/34 patients (62%) who had experienced diarrhea during their first episode relapsed in the second episode and 9/24 patients (38%) who had experienced CABS during their first episode of neutropenia relapsed in the second episode.

Transfer to intensive care was documented in 41/359 (11%) first episodes of neutropenia and in 54/521 (10%) overall episodes of neutropenia. Death occurred in 17/359 (5%) first episodes and 20/521 (4%) overall episodes.

Diarrhea

In 14/160 patients (9%) with diarrhea during their first episode of neutropenia, a potentially causative pathogen could be identified: *C. difficile* in eight patients, Rotavirus in four patients, and Adenovirus and Norovirus in one patient each. One patient with Norovirus and one patient with *C. difficile* were positive for the same pathogens in a consecutive episode of neutropenia. Other causative agents of diarrhea identified in consecutive episodes included *C. difficile* (n=4), Rotavirus (n=1), Norovirus (n=1) and *enteroaggregative E. coli* (n=1).

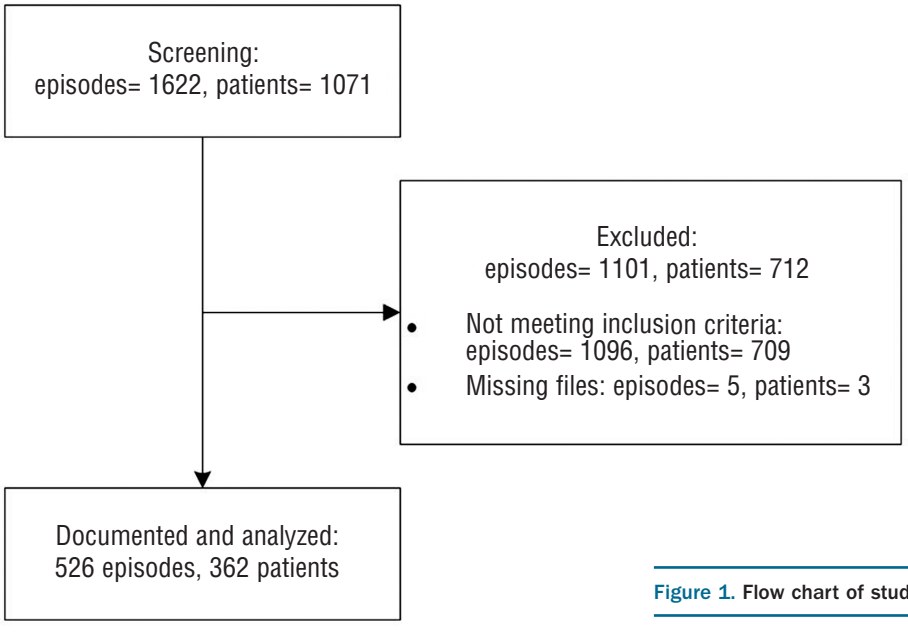

Figure 1. Flow chart of study progress.

Table 1. Indications for chemotherapy and cytostatic agents administered during first episodes of neutropenia.

Characteristic	Overall (n=359)
Indication for chemotherapy – n. (%)	
Acute myelogenous leukemia	120 (33)
Acute lymphoblastic leukemia	38 (11)
Non-Hodgkin's lymphoma	91 (25)
B-cell non-Hodgkin's lymphoma	73 (20)
T-cell non-Hodgkin's lymphoma	18 (5)
Hodgkin's lymphoma	27 (8)
Multiple myeloma	61 (17)
Solid tumors	19 (5)
Others*	9 (3)
Type of chemotherapy - n. (%)	
Pyrimidine anti-metabolites	223 (62)
Cytarabine >3 g/m^2	68 (19)
Steroids	218 (61)
Nitrogen mustard alkylating agents	187 (52)
Cyclophosphamide >50 mg/kg, Ifosfamide >10000 mg/m^2, Melphalan >200 mg/m^2	12 (3)
Anthracyclines	129 (36)
Topoisomerase inhibitors	99 (28)
Vinca alkaloids	63 (18)
Alkylating nitrosourea compounds	55 (15)
Methotrexate	53 (15)
>1000 mg/m^2	19 (5)
Rituximab	51 (14)
Mitoxantrone	39 (11)
Purine anti-metabolites	36 (10)
Platinum analogs	21 (6)
PEG-Asparaginase	10 (3)
Tretinoin	10 (3)
Other†	29 (8)

**Chronic lymphoblastic leukemia=6, Chronic myelogenous leukemia=3 †Hydroxyurea=6, Azacitidine=3, Imatinib=3, PK 412 vs. Placebo=3, Bleomycin=4, Bortezomib=2, Clofarabine=2, Nilotinib=2, Teniposide=2, Alemtuzumab=1, Sorafenib=1.*

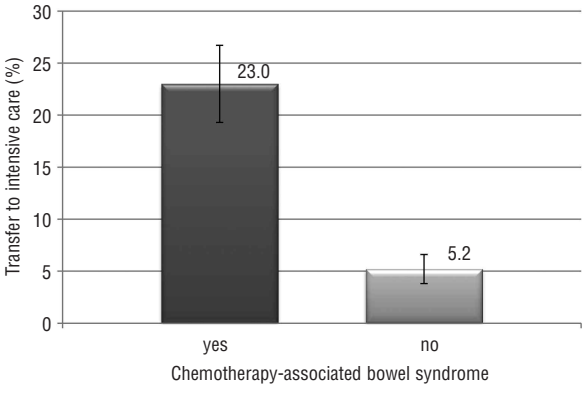

Figure 2. Absolute increase in the risk of transfer to intensive care in patients with chemotherapy-associated bowel syndrome (*P*<0.0001). Error bars denote the standard error of proportion (Wilson's method).

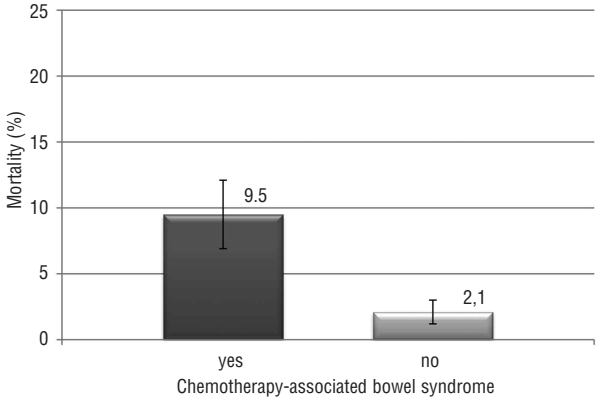

Figure 3. Absolute increase in mortality in patients with chemotherapy-associated bowel syndrome (*P*<0.0043). Error bars denote the standard error of proportion (Wilson's method).

Chemotherapy-associated bowel syndrome

Backward-stepwise binary logistic regression analysis yielded duration of neutropenia as the only risk factor for CABS (*P*<0.001; OR 1.067/d; 95% CI 1.026-1.110). In 124/161 episodes (77%) of neutropenia with documented CABS, C-reactive protein values were documented within 3 days prior to and after the diagnosis of CABS. For 124 episodes, the comparison of mean maximum values in these two time periods (before, 109 mg/L; after, 197 mg/L) by t-test showed a significant rise in C-reactive protein in the 3 days after the diagnosis of CABS (*P*<0.001; 95% CI 67-109 mg/L). Figures 2 and 3 show the absolute increase in the risk of transfer to intensive care and dying in patients with CABS.

Most patients who fulfilled the criteria for CABS and for whom a pathogen was identified from a stool sample also presented with diarrhea (95%). Only patient who tested positive for *C. difficile* had signs of CABS alone.

A pathological abdominal imaging result was documented in 23/161 neutropenic episodes (14%) with a clinical presentation of CABS and in 23/521 overall episodes of neutropenia (4.4%). Imaging methods included abdominal ultrasound (n=17), X-ray of the abdomen (n=10) and computed tomography of the abdomen (n=10). Documented pathological findings included pneumointestine (n=1), air-fluid levels (n=3), ileus (n=5), peritoneal cavity fluid (n=7), enterocolitis not further specified (n=13), and intestinal wall thickening (n=19). In seven cases of intestinal wall thickening, the extent was specified (mean, 15 mm; range, 4-60 mm). Colectomy was performed in 2/359 (1%) first episodes of neutropenia. There were no additional colectomies during consecutive episodes.

In 52/161 episodes (32%) of neutropenia with CABS, a positive blood culture was recorded. In the case of coagulase-negative staphylococci, only repeatedly positive cultures were considered. Isolates were distributed as follows: coagulase-negative staphylococci (n=13), *E. faecium* (n=12), and Gram-negative rods (n=26). Of these 26 blood cultures, ten displayed resistance to third-generation cephalosporins (i.e. *Pseudomonas aeruginosa*, *Acinetobacter baumanii*,

Capnocytophaga sputigena, *Brevundimonas diminuta* and ESBL-producers).

Risk factors for transfer to intensive care and death

Table 2 shows the results of backward-stepwise binary logistic regression analysis assessing potential risk factors for the endpoints "transfer to intensive care" and "death". After multivariate analysis, only duration of neutropenia and occurrence of CABS were identified as risk factors for "transfer to intensive care" with associated odds ratios of 1.061 (95% CI 1.021-1.103) and 4.753 (95% CI 2.297-9.833), respectively.

Concerning "death", administration of mitoxantrone and occurrence of CABS were identified as risk factors with associated odds ratios of 4.611 (95% CI 1.573-13.515), and 3.628 (95% CI 1.169-11.256), respectively.

Discussion

This is the first study to assess the epidemiology, treatment and clinical outcome of chemotherapy-associated abdominal complications in a multicenter approach. Our analysis shows a significant association between a clinical bedside rule for detection of CABS – defined as a combination of fever (T ≥37.8 °C) and abdominal pain and/or lack of bowel movement for at least 72 h – and an increased mortality in patients with chemotherapy-induced neutropenia lasting at least 5 days. Mitoxantrone was also associated with an increased risk of death. This is a plausible finding, since mitoxantrone was exclusively administered as part of induction chemotherapy for acute myelogenous leukemia, a regimen associated with a particularly high risk of complications. At the same time, mitoxantrone administration was not associated with the occurrence of CABS, thus underlining the independence of the latter as a risk factor.

Duration of neutropenia is a well-established risk factor for infectious complications.[24] In our study, duration of neutropenia was associated with the occurrence of CABS. However, the multivariate analysis of risk factors for transfer to an intensive care unit and death identified CABS as an independent risk factor, while – among others - duration of neutropenia was less powerful or even refused as a predictor of these events. This underlines that CABS is indeed a distinct risk factor for patients' morbidity and mortality.

In a prior meta-analysis by Gorschlüter *et al.*, neutropenic enterocolitis was defined as a combination of fever, abdominal pain and bowel wall thickening in any segment on ultrasound or computed tomography studies.[10] A pooled incidence of neutropenic enterocolitis was reported to be 5.3% in a population of hematology and oncology patients.[10] In comparison, the incidence of CABS in our study was 126/359 (35%) in first episodes of neutropenia and 161/521 (31%) in all episodes. Gorschlüter's criteria of neutropenic enterocolitis were fulfilled in 23/521 episodes (4.4%). Our clinical rule for CABS was designed to identify patients at an early pathophysiological stage of intestinal impairment. Considering that not all patients with abdominal symptoms eventually progress to develop neutropenic enterocolitis, the higher rate of CABS than of neutropenic enterocolitis was to be expected.

Of note, diarrhea alone was not associated with an increased risk of transfer to the intensive care unit or death. The incidence rates of 45% during first episodes and 40% during all episodes were well within the range of 19-67% found in prior observational studies in hematology/oncology patients.[4,6,9]

It is conceivable that some risk factors for the development of CABS or for death were not detected by our analysis. We tried to minimize this risk by including diverse underlying diseases and treatment regimens, and using a multicenter approach and a large sample of patients. Being a non-interventional study, some potential dispositional factors, e.g. genetic risk factors, could not be considered for the analysis.

In contrast to current reports of increasing incidence rates of *C. difficile*-associated diarrhea, in this study we documented only a moderate incidence of 5% during first episodes of neutropenia.[25,26] The same was true for the incidence of *C. difficile* in patients with CABS (6%). These findings are in line with results from Avery *et al.*, who recently reported a 5% incidence of *C. difficile*-associated diarrhea in 61 patients with diarrhea after autologous stem cell transplantation.[6] A second study reported an incidence rate of 7% in 875 chemotherapy-associated neutropenic episodes lasting at least 5 days.[8] Both publications, however, described a time period prior to the emergence of the epidemic *C. difficile* strain NAP1/027. Since 2003, this strain has been repeatedly described as the cause of hospital out-

Table 2. Results of backward-stepwise binary logistic regression analysis assessing risk factors for "transfer to intensive care" and "death".

Dependent variable: transfer to intensive care	univariate	multivariate (only remaining variables)	
Variable	*P* value	Odds Ratio	95% CI
Age	0.570		
AML or MDS	0.124		
Acute lymphoblastic leukemia	0.850		
Anthracyclines	0.144		
Diarrhea	0.576		
Duration of neutropenia	0.000	1.061*	1.021-1.103
Fever	0.025		
High dose cytarabine (>3g/m²)	0.572		
Mitoxantrone	0.154		
CABS	0.000	4.753	2.297-9.833
Constant	0.000	0.026	n.a.
Dependent variable: death	**univariate**	**multivariate (only remaining variables)**	
Variable	*P* value	Odds Ratio	95% CI
Age	0.096		
AML or MDS	0.477		
Acute lymphoblastic leukemia	0.875		
Anthracyclines	0.271		
Diarrhea	0.765		
Duration of neutropenia	0.028		
Fever	0.123		
High dose cytarabine (>3 g/m²)	0.247		
Mitoxantrone	0.010	4.611	1.573-13.515
CABS	0.002	3.628	1.169-11.256
Constant	0.000	0.022	n.a.

*AML: acute myelogenous leukemia; *per day, CABS: chemotherapy-associated bowel syndrome; MDS: myelodysplastic syndrome.*

breaks with high morbidity and mortality rates in North America and Europe.[27-29]

In contrast to these reports, a third observational study from 2007, including only hematology/oncology patients, found a comparatively high rate of *C. difficile* in 8/48 patients (17%) with diarrhea and in 1/11 patients (9%) with neutropenic enterocolitis.[4] Given the small number of patients in that single-center study, the differences from our study are hardly significant and may be caused by differences in local epidemiology.

In conclusion, our study succeeded in quantifying the relevance of CABS as a complication in hematology/oncology patients and provides a bedside rule that allows prediction of adverse outcomes. This clinical rule could be of key significance in the design of interventional clinical trials,[30] allowing the development of prophylactic and therapeutic strategies based on easily available criteria. The intervention assessed in such a study remains to be defined. Given the low number of anaerobic infections in the study population, the common approach of empirical metronidazole treatment does not seem promising. However, the cases of bacteremia observed during the present study may hint at the potential of empirical antibiotic regimens. Other potential approaches include the reduction of intestinal bacterial colonization or targeted intestinal colonization with non-pathogenic bacteria.

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

Financial and other disclosures provided by the authors using the ICMJE (www.icmje.org) Uniform Format for Disclosure of Competing Interests are also available at www.haematologica.org.

References

1. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2011;52(4):427-31.
2. Segal BH, Freifeld AG, Baden LR, Brown AE, Casper C, Dubberke E, et al. Prevention and treatment of cancer-related infections. J Natl Compr Canc Netw. 2008;6(2):122-74.
3. Maschmeyer G, Beinert T, Buchheidt D, Cornely OA, Einsele H, Heinz W, et al. Diagnosis and antimicrobial therapy of lung infiltrates in febrile neutropenic patients: Guidelines of the infectious diseases working party of the German Society of Haematology and Oncology. Eur J Cancer. 2009;45(14):2462-72.
4. Aksoy DY, Tanriover MD, Uzun O, Zarakolu P, Ercis S, Erguven S, et al. Diarrhea in neutropenic patients: a prospective cohort study with emphasis on neutropenic enterocolitis. Ann Oncol. 2007;18(1):183-9.
5. Altclas J, Requejo A, Jaimovich G, Milovic V, Feldman L. Clostridium difficile infection in patients with neutropenia. Clin Infect Dis. 2002;34(5):723.
6. Avery R, Pohlman B, Adal K, Bolwell B, Goldman M, Kalaycio M, et al. High prevalence of diarrhea but infrequency of documented Clostridium difficile in autologous peripheral blood progenitor cell transplant recipients. Bone Marrow Transplant. 2000;25(1):67-9.
7. Cartoni C, Dragoni F, Micozzi A, Pescarmona E, Mecarocci S, Chirletti P, et al. Neutropenic enterocolitis in patients with acute leukemia: prognostic significance of bowel wall thickening detected by ultrasonography. J Clin Oncol. 2001;19(3):756-61.
8. Gorschluter M, Glasmacher A, Hahn C, Schakowski F, Ziske C, Molitor E, et al. Clostridium difficile infection in patients with neutropenia. Clin Infect Dis. 2001;33(6):786-91.
9. Gorschluter M, Marklein G, Hofling K, Clarenbach R, Baumgartner S, Hahn C, et al. Abdominal infections in patients with acute leukaemia: a prospective study applying ultrasonography and microbiology. Br J Haematol. 2002;117(2):351-8.
10. Gorschluter M, Mey U, Strehl J, Ziske C, Schepke M, Schmidt-Wolf IG, et al. Neutropenic enterocolitis in adults: systematic analysis of evidence quality. Eur J Haematol. 2005;75(1):1-13.
11. Schalk E, Bohr UR, Konig B, Scheinpflug K, Mohren M. Clostridium difficile-associated diarrhoea, a frequent complication in patients with acute myeloid leukaemia. Ann Hematol. 2009 Jun 17. [Epub ahead of print]
12. Gorschluter M, Glasmacher A, Hahn C, Leutner C, Marklein G, Remig J, et al. Severe abdominal infections in neutropenic patients. Cancer Invest. 2001;19(7):669-77.
13. Bilgrami S, Feingold JM, Dorsky D, Edwards RL, Bona RD, Khan AM, et al. Incidence and outcome of Clostridium difficile infection following autologous peripheral blood stem cell transplantation. Bone Marrow Transplantation. 1999;23(10):1039-42.
14. Leung S, Metzger BS, Currie BP. Incidence of Clostridium difficile infection in patients with acute leukemia and lymphoma after allogeneic hematopoietic stem cell transplantation. Infect Control Hosp Epidemiol. 2010;31(3):313-5.
15. Delaunoit T, Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Findlay BP, et al. Mortality associated with daily bolus 5-fluorouracil/leucovorin administered in combination with either irinotecan or oxaliplatin: results from Intergroup Trial N9741. Cancer. 2004;101(10):2170-6.
16. Kuebler JP, Colangelo L, O'Connell MJ, Smith RE, Yothers G, Begovic M, et al. Severe enteropathy among patients with stage II/III colon cancer treated on a randomized trial of bolus 5-fluorouracil/leucovorin plus or minus oxaliplatin: a prospective analysis. Cancer. 2007;110(9):1945-50.
17. Sloan JA, Goldberg RM, Sargent DJ, Vargas-Chanes D, Nair S, Cha SS, et al. Women experience greater toxicity with fluorouracil-based chemotherapy for colorectal cancer. J Clin Oncol. 2002;20(6):1491-8.
18. Davila M, Bresalier RS. Gastrointestinal complications of oncologic therapy. Nat Clin Pract Gastr. 2008;5(12):682-96.
19. Buyukasik Y, Ozcebe OI, Haznedaroglu IC, Sayinalp N, Soylu AR, Ozdemir O, et al. Neutropenic enterocolitis in adult leukemias. Int J Hematol. 1997;66(1):47-55.
20. Wade DS, Nava HR, Douglass HO, Jr. Neutropenic enterocolitis. Clinical diagnosis and treatment. Cancer. 1992;69(1):17-23.
21. Jones GT, Abramson N. Gastrointestinal necrosis in acute leukemia: a complication of induction therapy. Cancer Invest. 1983;1(4):315-20.
22. DRKS. Deutsches Register Klinischer Studien. 2010 [cited 2010 22.12.2010]; Available from: https://drks-neu.uniklinik-freiburg.de/drks_web/
23. Vehreschild JJ, Rüping MJ, Farowski F, Cornely OA. ClinicalSurveys.net – A web-based research portal for rare infectious diseases. Mycoses. 2009;52:391.
24. Bodey GP, Buckley M, Sathe YS, Freireich EJ. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann Intern Med. 1966;64(2):328-40.
25. Kuijper EJ, van Dissel JT, Wilcox MH. Clostridium difficile: changing epidemiology and new treatment options. Curr Opin Infect Dis. 2007;20(4):376-83.
26. Rupnik M, Wilcox MH, Gerding DN. Clostridium difficile infection: new developments in epidemiology and pathogenesis. Nat Rev Microbiol. 2009;7(7):526-36.
27. Kuijper EJ, Barbut F, Brazier JS, Kleinkauf N, Eckmanns T, Lambert ML, et al. Update of Clostridium difficile infection due to PCR ribotype 027 in Europe, 2008. Euro Surveill. 2008;13(31). pii: 18942.
28. McDonald LC, Killgore GE, Thompson A, Owens RC, Jr., Kazakova SV, Sambol SP, et al. An epidemic, toxin gene-variant strain of Clostridium difficile. N Engl J Med. 2005;353(23):2433-41.
29. Warny M, Pepin J, Fang A, Killgore G, Thompson A, Brazier J, et al. Toxin production by an emerging strain of Clostridium difficile associated with outbreaks of severe disease in North America and Europe. Lancet. 2005;366(9491):1079-84.
30. Viscoli C, Bruzzi P, Glauser M. An approach to the design and implementation of clinical trials of empirical antibiotic therapy in febrile and neutropenic cancer patients. Eur J Cancer. 1995;31A(12):2013-22.