Acta Haematologica Polonica 2022
Number 4, Volume 53, pages 258–266
DOI: 10.5603/AHP.a2022.0033
ISSN 0001–5814
e-ISSN 2300–7117

ORIGINAL RESEARCH ARTICLE

Neutropenic enterocolitis and multidrug-resistant bacteria colonization in lymphoma patients undergoing autologous stem cell transplantation

Monika Joks*, Joanna Rupa-Matysek, Magdalena Matuszak, Anna Łojko-Dankowska, Lidia Gil

Department of Hematology and Bone Marrow Transplantation, Poznan University of Medical, Poznań, Poland

Abstract

Introduction: There is little iterature data regarding neutropenic enterocolitis (NE) development after autologous hematopoietic cell transplantation (auto-HCT) in non-Hodgkin lymphoma (NHL) patients. The aim of this study was to determine the incidence, risk factors, and clinical outcome of NE after auto-HCT in NHL patients with respect to the impact of multidrug-resistant Gram-negative bacteria (MDRG) and vancomycin-resistant enterococci colonization on the early outcome after auto-HCT.

Material and methods: This retrospective single-center analysis included a total of 65 NHL patients who underwent auto-HCT after BEAM (BCNU, etoposide, cytosine arabinoside, melphalan) conditioning (BEAM-auto-HCT).

Results: NE was diagnosed in nine (13.8%) patients, a median four days after auto-HCT. In 6/9 (66%) patients, septic shock following NE was diagnosed. In univariate analysis, MDRG colonization before BEAM-auto-HCT was the only factor significant for NE development [odds ratio (OR) 2.4 (1.14–5.0), $p = 0.027$], although this was not confirmed in multivariate analysis. Additionally, NE [OR 5.2 (1.9–13.9), $p = 0.001$] and MDRG colonization prior to transplant [OR 2.7 (1.0–7.0), $p = 0.041$] were independent factors for septic shock development.

Conclusions: Our findings suggest that NHL patients presenting with MDRG colonization before transplant should be kept under careful surveillance because of the high risk of the development of early severe infectious complications, including abdominal ones.

Key words: colonization, multidrug-resistant bacteria, neutropenic enterocolitis

Acta Haematologica Polonica 2022; 53, 4: 258–266

Introduction

Neutropenic enterocolitis (NE) is a life-threatening complication occurring in patients in the course of neoplastic and non-neoplastic diseases, mainly after chemotherapy [1, 2]. Retrospective data on NE incidence and mortality varies significantly from 0.8% up to 26% and 32–50% respectively. This reflects differences according to its definition, diagnostic criteria, and ultimately, treatment. Some historical data suggests that NE incidence is underestimated [1, 3]. The exact pathogenesis of NE is probably multifactorial, and is still incompletely understood. The main factors related to its development are mucosal injury and impaired immunity including neutropenia. Chemotherapeutic agents such as cytarabine, gemcitabine, vincristine, etoposide, doxorubicin and others can directly damage mucosa or predispose to

*Address for correspondence: Monika Joks, Department of Hematology and Bone Marrow Transplantation, Poznan University of Medical Sciences, Szamarzewskiego 84, 60–569 Poznań, Poland, phone +48 854 93 50 e-mail: mjoks@tlen.pl

Received: 03.04.2022 Accepted: 07.05.2022

intestinal distension and necrosis, and may cause impairment of intestinal motility. The initial mucosal injury leads to intestinal edema, vascular dilatation, mucosal disruption, and bacterial intramural invasion. Moreover, intestinal infiltration by malignant cells may also be responsible for the pathogenesis of NE. The pathological features of NE include patchy necrosis, hemorrhages, ulcers, edemas, perforations, infiltrating microorganisms and depletion of neutrophils. The spectrum of pathogens involved in NE development include mainly Gram-negative bacteria, but also Gram-positive bacteria, fungi and viruses [4, 5].

Literature data is scarce concerning NE incidence after auto-HCT. It has been suggested that there is a higher incidence of NE after autologous hematopoietic cell transplantation (auto-HCT) in patients with non-Hodgkin lymphoma (NHL) (18.8%) when compared to other hematological malignancies [1]. In recent years, a lot of data on the role of rectal colonization with multidrug-resistant bacteria has been published, but its significance in NHL patients who have undergone auto-HCT has not been specifically investigated.

The aim of our study was to estimate the incidence, risk factors and clinical outcome of NE in NHL patients after auto-HCT with BEAM (BCNU, etoposide, cytosine arabinoside, melphalan) conditioning (BEAM-auto-HCT), with an emphasis on the significance of multidrug-resistant bacteria (MDR) rectal colonization.

Material and methods

Our retrospective analysis included 65 adult patients with NHL who underwent BEAM-auto-HCT in one transplant center between July 2013 and December 2018. Exclusion criteria from analysis involved conditioning other than BEAM chemotherapy and a history of chronic bowel disease or abdominal surgery.

Complication profile and the outcome of procedure were analyzed from the first day of conditioning up to day 30 post-transplant.

The Bioethical Committee of Poznan University of Medical Sciences approved this study in accordance with the Declaration of Helsinki (KB no 934/20).

Transplant procedures

Standard evaluation of patients qualified for auto-HCT and disease-specific assessment was performed within 30 days before transplant. Peripheral blood stem cells were mobilized and collected after chemotherapy, followed by recombinant granulocyte colony-stimulating factor (G-CSF). Patients were uniformly conditioned with a BEAM regimen (dexamethasone 24 mg/m^2 on days –8 to –2, carmustine 300 mg/m^2 on day –8, etoposide 200 mg/m^2 on days –7 to –4, cytarabine 2 × 3,000 mg/m^2 on day –3, and melphalan 140 mg/m^2 on day –2). All patients received a low-germ diet and were housed in single air-filtered rooms on a dedicated transplantation unit, with intensified hygiene measures (masks, gloves, and gowns for staff; water and air control; limited visits). The BEAM-auto-HCTs were performed according to the local procedure with routinely inserted central venous catheters and anti-infective prophylaxis with fluconazole and acyclovir until neutrophil engraftment.

Definitions

Severe neutropenia was defined as absolute neutrophil count (ANC) <0.5 G/L.

Neutropenic fever was defined as a one-time oral temperature of greater than 38.3 °C (approximately 100.9 °F) or a sustained temperature of greater than 38 °C (100.4 °F) for ≥1 h in a patient with an ANC <0.5 G/L or an ANC expected to decrease to <0.5 G/L within 48 h [6].

Infections occurring during neutropenia were classified as: microbiologically documented (MDI) when the pathogenic microorganism was diagnosed; as clinically documented (CDI) with the presence of signs and symptoms of inflammation at anatomic sites and non-recovered pathogen; or as fever of unknown origin (FUO) in cases of fever without a localized source of infection or identified pathogen [7].

Bloodstream infection (BSI) was defined as a laboratory-confirmed positive blood culture. In the case of potential common skin commensals such as coagulase-negative *Staphylococci*, *Corynebacterium species* other than *Corynebacterium dyphteriae*, *Bacillus species* other than *Bacillus anthracis*, *Micrococcus*, *etc.*, it was deemed necessary to draw at least two consecutive positive blood cultures on different occasions [8]. Catheter-related blood stream infection (CR-BSI) was diagnosed according to the Infectious Diseases Society of America (IDSA) recommendations [9].

Multidrug-resistant Gram-negative bacteria (MDRG) were considered in those cases which were not susceptible to at least three of the following antimicrobial categories: antipseudomonal penicillins, cephalosporins, carbapenems, aminoglycosides and fluoroquinolones [10]. A diagnosis of invasive fungal infection was based on the European Organization for Research and Treatment of Cancer (EORTC)/Mycoses Study Group (MSG) criteria [11].

Microbiological procedures

In the event of fever, blood cultures from the catheter and peripheral vein and cultures from the possibly infected sites were taken. The blood samples were injected into BacT/ /Alert FN and BacT/Alert FA culture media. Analyses were performed using a computerized system for monitoring blood cultures (BacT/Alert 3D BioMérieux, France). In the case of diarrhea, stool cultures and tests for Clostridioides difficile antigen and toxin were performed (TECHLABC.DIFF QUIK CHEK COMPLETE® test). Additionally, culture swabs with amies collection (Eurotubo Collection Swab, Delta Lab) were taken from the suspected sites and routinely

screened for vancomycin-resistant enterococci (VRE) and MDRG from the rectum before transplant and thereafter weekly until neutrophil recovery. Rectal swabs and stool samples were inoculated onto screening plates consisting of chromID® VRE Agar, chromID®CARBA SMART Agar (BioMérieux) and examined for growth after 24–48 h of incubation at a temperature of 37°C. Purple colonies on chromID VRE were presumptively identified as VRE. After Gram staining, positive cocci were then subcultured to sheep blood agar and incubated at 37°C in a normal atmosphere, and examined after 24 h. In addition to colony morphology and Gram staining, catalase reaction, and the Vitek GP (BioMérieux) test was used to identify the enterococci at species level. The susceptibility of *Enterococcus spp.* isolates to vancomycin was tested by use of the disk diffusion method. This method was performed according to the European Committee on Antimocrobial Susceptibility (EUCAST) standard. Colonies of Gram-negative rods grown on the selective chromogenic medium were presumptively identified as MDRG. The identification and drug sensitivity of the cultured microorganisms were conducted using the Vitek 2 Compact system (BioMérieux) with standard interpretation of susceptibility according to the EUCAST. To detect extended-spectrum-β-lactamase strains (ESBL), the phenotype method double-disk synergy test was used. A two-step algorithm to detect carbapenemases was performed: carbapenems hydrolysis using the Rapidec®Carba NP test (BioMérieux) followed by polymerase chain reaction (PCR) — the loop-mediated isothermal amplification (LAMP) method (AmplexDiagnostics GmbH, Germany) to detect the genes for carbapenemases: NDM, VIM, IMP, OXA-48 like, KPC, OXA-23, OXA-40, OXA-58. For some pathogens, sensitivity was estimated using the E-test. Susceptibility for colistin was performed with the use of the microdilution method (SenstTest Colistin Liofilchem). All patients were also screened with biweekly galactomannan testing during the neutropenia period.

Neutropenic enterocolitis

NE was suspected in febrile neutropenic patients with abdominal pain and/or diarrhea, vomiting, guarding or ileus. The diagnostics included abdominal ultrasound (US) and the extended microbiology as described above. Sonography was performed in all patients suspected for NE with the use of a GE Voluson 730 at the patient's bedside with a standard scanning technique of the abdomen within 24 h of the onset of symptoms. Plain abdominal radiography, abdominal computed tomography (CT) or surgical assessment were planned only in the event of a suspicion of surgical complications or an unclear US result. NE was diagnosed according to the Gorschluter criteria, including bowel wall thickening >4 mm on US or CT in patients with neutropenic fever and symptoms of abdominal infection [3]. *Clostridioides difficile* enterocolitis was not classified as NE.

Statistical analysis

Descriptive statistics were used to present the parameters of the analyzed group. The ShapiroWilk test was performed to assess normal distribution. To compare the general characteristics of patients with and without NE, the chi square test was used for categorical variables and the Mann-Whitney U test for continuous variables. Similar analysis was performed to determine the impact of NE and MDRG colonization before transplant on early clinical outcome and severe complication incidence.

Univariate analysis for each potential risk factor was performed using logistic regression. Factors for which the *p*-value was <0.10 in univariate analysis were submitted to a multivariate conditional logistic regression model. Backward stepwise regression procedures were used to develop the final multivariate model. The probabilities of survival were estimated by the Kaplan–Meier method, and univariate comparisons were performed using the log-rank test. A *p*-value <0.05 was considered as significant. Odds ratios (ORs) and 95% CIs (confidence intervals) were calculated on the basis of the final model. The statistical analyses were performed with STATISTICA 13 and STATISTICA Medical Package 2.0 (StatSoft, Inc., Tulsa, OK, USA).

Results

The patients' clinical characteristics are set out in Table I.

Hematological recovery occurred in 62 (95%) patients, with neutrophil reconstitution on median day 11 (range 6–18). Three patients died before engraftment due to septic shock caused by *Pseudomonas aeruginosa* VIM (Verona Integron-encoded metallo-β-lactamase) on median day 7. The median duration of severe neutropenia was nine (range 8–21) days. Febrile neutropenia was observed in 59 (90%) patients. The characteristics of the neutropenic infections are set out in Table II.

NE was diagnosed in nine (14%) patients with a median time of incidence of four (range 2–7) days after BEAM-auto-HCT. All NE patients had a fever with a median duration of five (range 3–14) days, diarrhea and abdominal pain that was predominantly localized in the right lower quadrant of the abdomen. US revealed bowel wall thicknesses in all cases ranging from 5 mm to 12 mm, and two patients presented with bowel walls >10 mm. Asymmetric thickening of the mucosal wall was mainly localized in the ileocecal region. In one patient, a hemorrhage from the lower part of the gastrointestinal tract (GI) occurred, but a colonoscopy performed after neutrophil recovery revealed no abnormalities. All patients were assessed by a surgeon although no surgical management was necessary in any of the cases of NE. The general characteristics of the NE patients, including detailed microbiological findings, are set out in Table III.

Table I. Patients' baseline characteristics

Characteristics	All patients, n = 65
Male gender	44 (68%)
Age, median	51 (19–67)
Histopathology	
ALCL ALK+	1
DLBCL	22
EATL	1
FL	10
MCL	19
MZL	5
PBL	1
PCNSL	1
PMBL	5
THL	1
No of prior lines of therapy	1–4
Indication for auto-HCT	
Consolidation	12
Refractory disease	32
Relapse of disease	21
Disease status before auto-HCT	
Complete remission	34
Partial remission	23
Stable disease	8
Source of stem cells	
PB	64
BM	1
VRE(+) colonization before auto-HCT	32
MDRG colonization before auto-HCT	34

ALCL — anaplastic large cell lymphoma; DLBCL — diffuse large B cell lymphoma; EATL — enteropathy associated T-cell lymphoma; FL — follicular lymphoma; MCL — mantle cell lymphoma; MZL — marginal zone lymphoma; PBL — plasmablastic lymphoma; PCNSL — primary central nervous system lymphoma; PMBL — primary mediastinal lymphoma; THL — triple hit lymphoma; auto-HCT— autologous hematopoietic cell transplantation; PB — peripheral blood; BM — bone marrow; VRE — vancomycin resistant enterococcus; MDRG — multidrug resistant Gram-negative bacteria

Table II. Neutropenic infections

Infection	All patients, n = 65
Fever	58 (89%)
FUO	7 (11%)
MDI	48 (74%)
CDI	3 (4.6%)
BSI	27 (41.5%)
Septic shock	7 (10.7%)
CRBSI	7 (10.7%)
Diarrhea	41 (63%)
NE	9 (13.8%)
Clostridioides difficile enterocolitis	1 (1.5%)
Pneumonia	7 (10.7%)
Urinary tract infection	5 (7.6%)
Aspergillosis	0
Influenza	0

FUO — fever of unknown origin; MDI — microbiologically documented infection; CDI — clinically documented infection; BSI — blood stream infection; CRBSI — catheter related blood stream infection; NE — neutropenic enterocolitis

In a total group of 65 pts, MDRG and VRE colonization was confirmed prior to the BEAM-auto-HCT in 20 (31%) and 22 (34%) patients respectively. All NE patients were colonized with MDRG before auto-HCT, and all produced extended spectrum beta-lactamase (ESBL) including nine patients with *Enterobacterales* colonization (two patients *Escherichia coli* and seven patients *Klebsiella pneumoniae*) and in one patient with ESBL-producing *Chryseobacterium indulogenes* as another pathogen. In our series, 7/9 NE patients were colonized with *Enterococci* including five cases of VRE forms (four *Enterococcus faecalis* and one *Enterococcus faecium*). Stool cultures revealed a wide spectrum of pathogens including those observed in rectal swabs and additional ones: ESBL-producing *Stenotrophomonas maltophilia*, VIM-producing *P. aeruginosa* and *Candida cruzei*. Classic enteric bacteria such as *Salmonella enterica, Shigella species, Yersinia species, Campylobacter species, Aeromonas species, Vibrio species, enterohemorrhagic Escherichia. coli* and viruses were not detected. Bloodstream infections were found in four patients with NE including two cases with MDRGs [ESBL-producing *K. pneumoniae* and VIM-producing *P. aeruginosa*] and two cases of *Enterococci* non-VRE.

All patients with NE were treated empirically with carbapenems and colistin. Vancomycin was given to six patients and linezolid to three. Moreover, three patients were treated additionally with amikacin, three with amphotericin, and two with tigecyline according to microbiological identification or the results of rectal swabs. All the patients received parenteral nutrition and G-CSF. Additionally, three patients received intravenous immunoglobulins. Septic shock occurred in 6/9 (66%) patients, and all cases were in the group with microbiologically documented NE. A fatal course of NE was observed in only one patient, who developed septic shock, paralytic ileus and bloody vomiting necessitating a nasogastric tube; the patient was referred to the intensive care unit (ICU) and ultimately died seven days after transplant. Patients with NE had a trend for shortened survival at day 30 after auto-HCT ($p = 0.078$).

Table III. Neutropenic enterocolitis patients' characteristics

Gender/age histopathology	No of prior therapy/ /status at autoHCT	NE- day after auto-HCT/ /thickness of wall	Neu reconstitution	VRE colonization prior to auto-HCT susceptibility	
M/55 MCL	4/CR	+4 d/7 mm	+10	*E. faecalis:* vancomycin, teicoplanin	
M/38 PMBL	4/PR	+5 d/6 mm	+18	*E. faecalis* VRE	
M/62 MCL	3/PR	+4 d/6 mm	+15	*E. faecalis* VRE	
F/58 DLBCL	3/SD	+7 d/5 mm	+12	*E. faecium* VRE	
M/43 PBL	1/CR	+3 d/5 mm	+11	*E. faecalis* VRE	
F/52 FL	3/CR	+2 d/8 mm	+13	No	
M/64 EATL	3/CR	+3 d/9 mm	+12	*E. faecalis* VRE	
M/51 MCL	1/CR	+5 d/5 mm	+13	*E. faecium*: gentamycin, vancomycin, teicoplanin	
M/61 MCL	2/PR	+7 d/11 mm	+11	No	

Ch. indulogenes — *Chryseobacterium indulogenes*; CR — complete remission; DLBCL — diffuse large B-cell lymphoma; EATL — enteropathy associated T-cell lymphoma; *E. faecium* — *Enterococcus faecium*; *E. faecalis* — *Enteroccus faecalis*; ESBL — extended spectrum β-lactamases; FL — follicular lymphoma; *K. pneumoniae* — *Klebsiella pneumoniae*; MCL — mantle cell lymphoma; ND — no data; PBL — plasmablastic lymphoma; *P. aeruginosa* — *Pseudomonas aeruginosa*; shd — susceptible for higher doses; PMBL — primary mediastinal B-cell lymphoma; PR — partial remission; VIM — Verona Integron-encoded metallo-β--lactamase; VRE — vancomycin resistant enterococci

Risk factor analysis

Risk factor analysis for NE incidence was performed with the following factors: gender, age, stage, indication for auto-HCT, number of prior lines of chemotherapy (≤2 vs. >2), diabetes mellitus, VRE or MDRG colonization before BEAM-auto-HCT, time of severe neutropenia, time to neutrophil recovery, and IgG levels before transplant.

Univariate analysis revealed that MDRG colonization before BEAM-auto-HCT was the only risk for NE development [OR 2.4; 95% CI 1.14–5.0, $p = 0.027$], although its independent significance was not confirmed in multivariate analysis.

Additional analyses revealed two factors significant for septic shock development: MDRG colonization before transplant [OR 3.2; 95% CI 1.47–6.975, $p = 0.0035$] and NE [OR 5.89; 95% CI 2.4–14.6, $p = 0.0001$]. Multivariate analysis confirmed the prognostic significances of NE [OR 5.2; 95% CI 1.9–13.9, $p = 0.001$] and MDRG colonization [OR 2.7; 95% CI 1.0–7.0, $p = 0.041$] for septic shock incidence.

Discussion

Our analysis is a continuation of the previous study on NE from our center, which was the first prospective study evaluating the incidence and risk factors of NE in a population of patients undergoing high dose therapy with subsequent

	MDRG colonization before auto-HCT susceptibility	Stool cultures susceptibility	BSI/pathogen	Septic shock	Alive/cause of death
	Ch. indulogenes ESBL(+): sulfametoxazole/trimetoprim, shd levofloxacin *K. pneumoniae* ESBL(+): imipenem, colistin, shd meropenem	*Ch. indulogenes* ESBL(+): sulfametoxazole/trimetoprim, shd levofloxacin *E. faecalis*: vancomycin, teicoplanin	No	No	Yes
	K. pneumoniae ESBL(+): *susceptible* — impenem, meropenem, colistin, shd amikacin	*K. pneumoniae* ESBL(+)	No	Yes	Yes
	K. pneumoniae ESBL(+): imipenem, meropenem, tigecilin, colistin shd amikacin	*K. pneumoniae* ESBL (+) *C. cruzei*	No	Yes	No PD (+ 11 months after auto-HSCT)
	K. pneumoniae ESBL(+): impenem, meropenem, colistin	S. *maltophilia* ESBL(+): levofloxacin, trimetoprim/ /sulfametoxazole	Yes *K. pneumoniae* ESBL(+)	No	Yes
	E. coli ESBL(+): imipenem, meropenem, etarpenem, amikacin, gentamycin, tobramycin	*P. aeruginosa* VIM: colistin *E. coli* ESBL(+) *Entrococcus faecalis* VRE	Yes *P. aeruginosa* VIM: colistin, shd, artreonam	Yes	No +7 d after auto-HSCT — NE, septic shock, bloody vomiting
	K pneumonia ESBL(+): imipenem, meropenem, amikacin, colistin, sulfametoksazol	ND	No	No	Yes
	K. pneumoniae ESBL(+): imipenem, colistin, shd meropenem	*K. pneumoniae* ESBL(+) *E. faecalis VRE*	No	Yes	Yes
	E. coli ESBL(+): piperacilin/tazo, meropenem, imipenem, amikacin, tigecilin, colistin	ND	Yes *E. faecium*: vancomycin, teicoplanin	Yes	Yes
	K. pneumoniae ESBL(+): imipenem, meropenem, amikacin	*K. pneumoniae* ESBL(+)	Yes *E. faecium*: vancomycin, teicoplanin	Yes	Yes

auto-HCT [1]. The research revealed a higher incidence of NE after auto-HCT in the group of NHLs patients compared to other malignancies. Based on this finding, we decided to investigate the incidence, risk factors and outcome for NE after auto-HCT in NHLs patients conditioned exclusively with BEAM therapy, with a special emphasis on the potential role of MDRG and VRE colonization.

In our study, NE was diagnosed in 14% of patients, which is comparable with previously reported rates in NHLs patients after transplant [1]. The reason for the last one may be related to the use of homogenous conditioning with the BEAM protocol which contains high-dose cytarabine and etoposide. Both agents have been known to induce GI mucosal damage, and the use of cytarabine has been associated with the development of NE in several studies [3, 12, 13]. Early development of NE after high dose chemotherapy seems to indicate the importance of the conditioning regimen in the development of NE, rather than the duration of neutropenia. Finally, lymphoma infiltration of the bowel wall cannot be definitively excluded, although patients undergoing auto-HCT are usually in at least partial remission [1]. The mortality rate in our study was significantly lower compared to the historical data mentioned above. This is probably due to early diagnosis and the appropriate intensive treatment and monitoring, although survival analysis on day 30 after transplant revealed that

patients with NE had a trend towards shortened survival (p = 0.078). Univariate analysis revealed MDRG colonization before BEAM-auto-HCT is the only risk for NE development, however, its significance was not confirmed in multivariate analysis. It is worth noting that all of the NE patients were colonized by ESBL-producing MDRG strains, mainly by ESBL-producing *K. pneumoniae,* 7/9 (77%), and furthermore that half of them were colonized with VRE. All the MDRGs were susceptible to colistin and imipenem, and some of them were sensitive to meropenem and amikacin given in high doses. This probably reflects the wide use of the listed antibiotics. When compared to our cohorts treated between 2006 and 2010, recent years have seen a noticeable increase of MDRG infections, and their resistance to fluoroquinolones is still being observed despite the discontinuation of the use of them in prophylaxis [1]. Literature data reports a dramatic increase in MDRs and pandrug-resistant bacteria (PDR) infections in neutropenic patients over the past decade. Gram-positive resistant bacteria include methicillin-resistant staphylococci and VRE. The most affected species in the group of resistant G-negative bacteria include

K. pneumoniae, E. coli, P. aeruginosa and Acinetobacter baumanii [14–20]. Among resistant *Enterobacterales,* the percentage of ESBL-producing *K. pneumoniae* strains exceeds 50% in several series, although this is lower for resistant *Escherichia coli*, varying from 11% to 69% in different countries [14, 15]. In HCT patients, the incidence of carbapenem-resistant (CR) *K. pneumoniae* infections showed a 6-fold increase in 2010–2013, reaching rates of 0.5% in autologous transplant and 2.9% in allogeneic transplant settings [16]. Of note, rectal colonization by CR *K. pneumoniae* was followed by BSIs in 45% of neutropenic patients [17].

Most of our NE patients, 6/9 (66%), experienced septic shock, but fortunately a fatal course was observed in only one case. Based on multivariate regression analysis, two factors were identified as significant for septic shock development such as MDRG colonization before transplant and NE. The most serious complications of MDR bacteria colonization, including BSI or septic shock, may be life-threatening and sometimes require ICU treatment. An Italian multicenter prospective study including 144 patients revealed the frequency of MDR colonization at admission to be 6.5%. MDR colonization increased the risks of both BSI and BSI by the same pathogen. The 3-month OS was significantly lower for patients colonized with MDR bacteria. CR-related BSI and a urinary catheter were independent predictors of death. The authors concluded that tailored empiric antibiotic treatment should be decided on the basis of colonization [20]. In our study, gut colonization at admission was more frequent, with rates of MDRGs and VRE colonization of 31% and 34% respectively. This difference may result from the fact that our patients were heavily pretreated and had experienced many previous hospitalizations. In cancer patients, mucosal barrier damage, usually most marked in the small intestine, is the result of underlying treatment. The mechanisms involved in this process include the release of pro-inflammatory cytokines and tissue enzymes resulting in apoptosis and tissue injury which allows for subsequent bacterial translocation and a subsequent increase in the incidence of bacteremia. It has been demonstrated that mucositis, rather than prolonged neutropenia, is responsible for a high rate of bacteremia in HCT recipients [21, 22]. There is some data suggesting the impact of MDR gut colonization on infectious complications incidence, especially BSI, and moreover an increased risk of acute graft-versus-host disease (GvHD) and higher mortality in patients after allogeneic hematopoietic cell transplantation (allo-HCT) [23–25]. Data is limited concerning MDR colonization on the clinical outcome after auto-HCT, originating from retrospective studies and patients with different hematological malignancies [26–28]. Interestingly, one of them reported increased early non-relapse mortality secondary to infectious complications in a lymphoma subgroup colonized with MDR [26]. None of studies mentioned above analyzed the relationship between MDR colonization and NE incidence. To the best of our knowledge, our study is the first to emphasize the key role of MDRG colonization in a homogenous group of NHL patients who have undergone BEAM-auto-HCT. Our study has its limitations, i.e. the retrospective character of the analysis, and the small group of patients.

Conclusions

In conclusion, our findings suggest that NHL patients presenting with MDRG colonization before transplant should be kept under careful surveillance because of the high risk of early severe infectious complications development, including abdominal ones.

Authors' contributions

MJ — concept, data collection and analysis, drafting article, statistics. JRM — data analysis and critical revision of article. AŁD, MM — critical revision of article. LG — critical revision and approval of article.

Conflict of interest

None.

Financial support

None.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments

involving humans; EU Directive 2010/63/EU for animal experiments; uniform requirements for manuscripts submitted to biomedical journals.

References

1. Gil L, Poplawski D, Mol A, et al. Neutropenic enterocolitis after high--dose chemotherapy and autologous stem cell transplantation: incidence, risk factors, and outcome. Transpl Infect Dis. 2013; 15(1): 1–7, doi: 10.1111/j.1399-3062.2012.00777.x, indexed in Pubmed: 22862907.
2. Davila ML. Neutropenic enterocolitis. Curr Treat Options Gastroenterol. 2006; 9(3): 249–255, doi: 10.1007/s11938-006-0043-2, indexed in Pubmed: 16901388.
3. Gorschlüter M, Mey U, Strehl J, et al. Neutropenic enterocolitis in adults: systematic analysis of evidence quality. Eur J Haematol. 2005; 75(1): 1–13, doi: 10.1111/j.1600-0609.2005.00442.x, indexed in Pubmed: 15946304.
4. Xia R, Zhang X. Neutropenic enterocolitis: a clinico-pathological review. World J Gastrointest Pathophysiol. 2019; 10(3): 36–41, doi: 10.4291/wjgp.v10.i3.36, indexed in Pubmed: 31692935.
5. Rodrigues FG, Dasilva G, Wexner SD. Neutropenic enterocolitis. World J Gastroenterol. 2017; 23(1): 42–47, doi: 10.3748/wjg.v23.i1.42, indexed in Pubmed: 28104979.
6. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Infectious Diseases Society of Americaa. 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): 427–431, doi: 10.1093/cid/ciq147, indexed in Pubmed: 21205990.
7. Gil L, Styczynski J, Komarnicki M. Infectious complication in 314 patients after high-dose therapy and autologous hematopoietic stem cell transplantation: risk factors analysis and outcome. Infection. 2007; 35(6): 421–427, doi: 10.1007/s15010-007-6350-2, indexed in Pubmed: 17926001.
8. CDC. Device associated module BSI. Bloodstream Infection Event (Central Line-Associated Bloodstream Infection and Non-central line-associated Bloodstream Infection. http://www cdc gov/nhsn/PDFs/pscManual/ 4PSC_CLABScurrent pdf (January 31, 2022).
9. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis. 2009; 49(1): 1–45, doi: 10.1086/599376, indexed in Pubmed: 19489710.
10. Gustinetti G, Mikulska M. Bloodstream infections in neutropenic cancer patients: a practical update. Virulence. 2016; 7(3): 280––297, doi: 10.1080/21505594.2016.1156821, indexed in Pubmed: 27002635.
11. Donnelly JP, Chen SC, Kauffman CA, et al. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. Clin Infect Dis. 2020; 71(6): 1367–1376, doi: 10.1093/cid/ciz1008, indexed in Pubmed: 31802125.
12. Albiger B, Glasner C, Struelens MJ, et al. European Survey of Carbapenemase-Producing Enterobacteriaceae (EuSCAPE) working group. Carbapenemase-producing Enterobacteriaceae in Europe: assessment by national experts from 38 countries, May 2015. Euro Surveill. 2015; 20(45), doi: 10.2807/1560-7917.ES.2015.20.45.30062, indexed in Pubmed: 26675038.
13. Cantón R, Akóva M, Carmeli Y, et al. European Network on Carbapenemases. Rapid evolution and spread of carbapenemases among Enterobacteriaceae in Europe. Clin Microbiol Infect. 2012; 18(5): 413–431, doi: 10.1111/j.1469-0691.2012.03821.x, indexed in Pubmed: 22507109.
14. Gudiol C, Bodro M, Simonetti A, et al. Changing aetiology, clinical features, antimicrobial resistance, and outcomes of bloodstream infection in neutropenic cancer patients. Clin Microbiol Infect. 2013; 19(5): 474–479, doi: 10.1111/j.1469-0691.2012.03879.x, indexed in Pubmed: 22524597.
15. Kim SH, Kwon JC, Choi SM, et al. Escherichia coli and Klebsiella pneumoniae bacteremia in patients with neutropenic fever: factors associated with extended-spectrum β-lactamase production and its impact on outcome. Ann Hematol. 2013; 92(4): 533–541, doi: 10.1007/s00277-012-1631-y, indexed in Pubmed: 23161391.
16. Girmenia C, Rossolini GM, Piciocchi A, et al. Infections by carbapenem-resistant Klebsiella pneumoniae in SCT recipients: a nationwide retrospective survey from Italy. Bone Marrow Transplant. 2014; 50(2): 282–288, doi: 10.1038/bmt.2014.231.
17. Giannella M, Trecarichi EM, De Rosa FG, et al. Risk factors for carbapenem-resistant Klebsiella pneumoniae bloodstream infection among rectal carriers: a prospective observational multicentre study. Clin Microbiol Infect. 2014; 20(12): 1357–1362, doi: 10.1111/1469-0691.12747, indexed in Pubmed: 24980276.
18. Cattaneo C, Antoniazzi F, Casari S, et al. P. aeruginosa bloodstream infections among hematological patients: an old or new question? Ann Hematol. 2012; 91(8): 1299–1304, doi: 10.1007/s00277-012-1424-3, indexed in Pubmed: 22349723.
19. Kim SB, Min YH, Cheong JW, et al. Incidence and risk factors for carbapenem- and multidrug-resistant Acinetobacter baumannii bacteremia in hematopoietic stem cell transplantation recipients. Scand J Infect Dis. 2014; 46(2): 81–88, doi: 10.3109/00365548.2013.857042, indexed in Pubmed: 24325335.
20. Cattaneo C, Di Blasi R, Skert C, et al. SEIFEM Group. Bloodstream infections in haematological cancer patients colonized by multidrug-resistant bacteria. Ann Hematol. 2018; 97(9): 1717–1726, doi: 10.1007/s00277-018-3341-6, indexed in Pubmed: 29705860.
21. Sonis ST, Elting LS, Keefe D, et al. Mucositis Study Section of the Multinational Association for Supportive Care in Cancer, International Society for Oral Oncology. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. Cancer. 2004; 100(9 Suppl): 1995–2025, doi: 10.1002/cncr.20162, indexed in Pubmed: 15108222.
22. Elting LS, Cooksley C, Chambers M, et al. The burdens of cancer therapy. Clinical and economic outcomes of chemotherapy-induced mucositis. Cancer. 2003; 98(7): 1531–1539, doi: 10.1002/cncr.11671, indexed in Pubmed: 14508842.
23. Bilinski J, Robak K, Peric Z, et al. Impact of gut colonization by antibiotic-resistant bacteria on the outcomes of allogeneic hematopoietic stem cell transplantation: a retrospective, single-center study. Biol Blood Marrow Transplant. 2016; 22(6): 1087–1093, doi: 10.1016/j.bbmt.2016.02.009, indexed in Pubmed: 26900084.
24. Sadowska-Klasa A, Piekarska A, Prejzner W, et al. Colonization with multidrug-resistant bacteria increases the risk of complications and a fatal outcome after allogeneic hematopoietic cell transplantation. Ann Hematol. 2018; 97(3): 509–517, doi: 10.1007/s00277-017-3205-5, indexed in Pubmed: 29255911.

25. Patriarca F, Cigana C, Dozzo M, et al. Risk factors and outcomes of infections by multidrug-resistant gram-negative bacteria in patients undergoing hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2017; 23(2): 333–339, doi: 10.1016/j.bbmt.2016.11.005, indexed in Pubmed: 27826061.
26. Scheich S, Reinheimer C, Brandt C, et al. Clinical impact of colonization with multidrug-resistant organisms on outcome after autologous stem cell transplantation: a retrospective single-center study. Biol Blood Marrow Transplant. 2017; 23(9): 1455–1462, doi: 10.1016/j.bbmt.2017.05.016, indexed in Pubmed: 28528711.
27. Kapur D, Dorsky D, Feingold JM, et al. Incidence and outcome of vancomycin-resistant enterococcal bacteremia following autologous peripheral blood stem cell transplantation. Bone Marrow Transplant. 2000; 25(2): 147–152, doi: 10.1038/sj.bmt.1702123, indexed in Pubmed: 10673672.
28. Ford CD, Lopansri BK, Gazdik MA, et al. The clinical impact of vancomycin-resistant Enterococcus colonization and bloodstream infection in patients undergoing autologous transplantation. Transpl Infect Dis. 2015; 17(5): 688–694, doi: 10.1111/tid.12433, indexed in Pubmed: 26256692.