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Incidence and Risk Factors of Neutropenic Enterocolitis after Myelosuppressive Chemotherapy

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Abstract

Background Neutropenic enterocolitis (NE) is a serious complication in patients receiving intensive chemotherapy for the treatment of onco-haematological diseases. Yet, the relative incidence of the disease and its risk factors among patients treated with different regimen is not well defined.

Methods The development of NE was analysed in 1223 neutropenic episodes from 692 onco-hematological patients receiving chemotherapy at the isolation Unit of CHUV who signed an informed consent (Swissethics 2017-01975). NE was defined by the presence abdominal signs and symptoms during neutropenic fever together with bowel wall thickening >4mm in any bowel segment by computed tomography or ultrasound. The incidence of NE and risk factors known at hospitalization baseline were analysed by using uni- and multivariate regression models according to the chemotherapy regimen, including those used for the induction of acute myeloblastic (AML) or lymphoblastic (ALL) leukemia and autologous hematopoietic cell transplantation (HCT).

Results. A total of 72 episodes of radiologically-proven NE (5.9%) occurred; the percentage of NE was 16.3% for AML induction (e.g. HOVON based protocol), 5.6% for autologous HCT using the BEAM protocol, 4.8% for ALL induction, 2.9% for AML salvage (e.g. CLAG or FLAG +/- idarubicin), 1.9% for autologous HCT using a non-BEAM protocol (e.g. melphalan) and 1.9% for the other types of chemotherapy (Figure 1). In the HCT population, the single independent risk factor for NE was the BEAM versus non-BEAM protocol (Odd ratio [OR]=3.40, 95% confidence interval [CI] 1.14-10.1, P=0.03). In AML patients, independent risk factors for NE included induction versus salvage chemotherapy (OR=3.87, CI 1.31-11.4, P=0.01),

chemotherapy with amsacrine (OR=2.94, CI 1.40-6.21, P=0.005) and triple intrathecal chemotherapy (OR=2.03, CI 1.01-4.08, P=0.048).

Conclusions. Susceptibility to NE is strongly influenced by the type of chemotherapy. Patients receiving salvage therapy for AML have a surprisingly low rate of NE, possibly due to the concomitant use of G-CSF or an immunomodulaor effect of fludarabine or cladribine. Intrathecal chemotherapy has probably not a direct effect on NE but reflect the patients with high-risk AML quickly neutropenic or presenting a leukemic digestive infiltration.

Introduction

Neutropenic enterocolitis (NE) is one of the most serious gastrointestinal complications in patients receiving intensive chemotherapy for the treatment of onco-hematological diseases. It affects about 5% of neutropenic patients with a mortality rate ranging from 10-63% (1-3, 6-9, 11, 14) and consists in segmental, stenosing inflammation of the gastrointestinal mucosa, particularly the ileum, caecum and ascending colon. NE is thought to result from a combined effect of cyto- and neuro-toxicity of chemotherapeutic agents, neutropenia, coagulation disorders and resident bacterial flora (6, 18, 20). Because of its high cellular renewal rate, the gastrointestinal mucosa is particularly sensitive to chemotherapeutic agents, and can be the site of cytotoxic lesions ranging from simple inflammation to loss of integrity, large ischemic necrosis and perforation. Neutropenia renders the mucosa particularly prone to bacterial or fungal translocation (11) leading to local infection (e.g. peritonitis) and/or bacteremia, sepsis and/or shock. Infections result from translocation of the resident flora, whose composition is influenced by antibiotics. Most pathogens include gram negative bacteria (*Escherichia Coli*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa* and other enterobacteria), gram-positive bacteria (V*iridians* streptococci and enterococococci) (1, 4, 5), as well as fungi (e.g. *Candida spp*) (2, 5, 7, 8). Additional factors can further contribute to the development of the disease; thrombocytopenia can lead to hemorrhage and compromise vascular supply and active leukemic infiltration can contribute to mucosal damage (1-6, 9, 14).

The diagnosis for NE has long been ill-defined, making it difficult to clinically distinguish NE from other abdominal infections (appendicitis, cholecystitis, diverticulitis, *Clostidium difficile* colitis, acute megacolon), local manifestations of

malignancy (relapse, local infiltration) or other conditions (graft-versus-host disease inflammatory bowel disease, intussusception, obstruction, ischemia). The current definition combines clinical and radiological criteria. The clinical criteria remain heterogeneous and unspecific, including any symptom suggestive of abdominal infection (i.e. diarrhea, nausea or vomiting, abdominal distention and right lower quadrant tenderness). The radiological criterion is more specific, considering bowel wall thickening >4mm detected by abdominal ultrasound (US) examination or computed tomography (CT); this 4mm cutoff is considered a reliable criterion, as such thickening is proven very uncommon in non-inflammatory bowel conditions after chemotherapy (4, 6, 9-11, 14, 17, 24-28).

The therapeutic guidelines are based on the recommendations of the Infectious Diseases Society of America (IDSA 2010). A conservative approach including fluid resuscitation, bowel rest, abdominal decompression and parenteral nutrition is indicated (1, 2, 4-9, 14). Broad-spectrum intravenous antibiotherapy must be initiated after hemocultures are taken and include a monotherapy with carbapenem or piperacillin-tazobactam or duotherapy with cefepime plus metronidazole. The duration of therapy is of 14 to 21 days, until neutrophil recovery and afebrile condition; resistance must be tested and the antibiotics switched when needed (1-6). In case of sepsis or sepsis shock, a therapy with amikacine and vancomycine should be added. In case of detection of candidemia or remain of febrile and neutropenic state despite empirical antibiotherpay for more than 5 days, most clinicians support antifungal intravenous therapy with caspofungine or amphotericin B (1, 2, 5, 7, 9). Surgery is justified in patients with necrotic or perforated segments of the bowel wall, uncontrolled bleeding, or presence of deterioration with uncontrolled sepsis despite adequate treatment. In that case, the standard surgical treatment is a two-stage right hemi-colectomy with removal of all necrotic segments (1, 4, 5, 9, 14). In high-risk

patients, such as those with profound neutropenia (<100/ml), hypotension, pneumonia or invasive fungal infection, it is recommended to give granulocyte colony stimulating factor (G-CSF), although no clinical study has yet verified the actual efficiency of this medication (1-3, 5, 6, 8, 9). In case of adverse outcome, such as sepsis or septic shock, a placement in the intensive care unit is supported.

The identification of risk factors of NE largely depends on multiple factors, in particular the type of clinical definition and study population. Many studies have used heterogeneous populations with different types of underlying disease and chemotherapy regimens. Those studies have also suggested that particular chemotherapeutic agents, such as cytarabine (2,4-6,9) and etoposide (2,4,5), but also anthracyclines (8), such as daunomycine (5, 9) and idarubicin (2, 6, 33), cyclophosphamide (2,4,9), gemcitabine (4), 5- florouracil (4), fludarabine and vincristine (9), taxanes (4), mitoxantrone (8) and platine (2,4), methotrexate (2,9) or carmustine (bis-chloroethylnitrosourea, BCNU, BiCNU), etoposide, cytarabine and melphalan (BEAM) protocol (3), are associated with NE. However, it is not clear from most studies whether NE directly results from the drug toxicity and/or from other drugs administered concomitantly. Prednisone might have an adverse effect because of its healing-delay-effect (1, 5, 6, 9). Other factors have been reported to influence the risk of NE, such as oncological features (relapse of leukemia, uncontrolled cancer, intestinal tumor invasion, previous abdominal surgery), co-morbid conditions (preexisting bowel abnormalities such as diverticulitis or polyposis, patient age or body max index), or clinical conditions (mucositis, thrombocytopenia or concomitant *Cl. Difficile* infection). Again, the heterogeneity among patients in such studies and the absence of multivariate models makes it difficult to determine which factor are independently associated with NE (2, 3, 5, 6, 15, 16), high-lightening the need for studies using homogeneous groups of patients and/or multivariate models.

The goal of this study was to determine the incidence of NE in a selected onco-hematological population, as well as the determination of risk factors correlated with NE in well-defined groups of patients at risk.

Methods

Study cohort and design. All adult neutropenic patients hospitalized from January 2007 to June 2017 in the Isolation Unit of Medicine at CHUV for an active malignancy such as acute myeloid or lymphoid leukemias (AML, ALL) or chronic myeloid or lymphoid leukemias (CML, CLL), Hodgkin and non-Hodgkin lymphomas (HL, NHL), multiple myeloma (MM), myelodysplastic syndrome (MDS) or aplastic anemia (AA), undergoing intensive chemotherapy and who signed an informed consent for contributing to a clinical research database were included (Swissethics 2017-01975). Clinical date were retrospectively collected, including demography (age, sex, ethnic group, co-morbidities, type of underlying hematologic malignancies, BMI, chemotherapeutic protocol) and systematic classification of neutropenic enterocolitis (duration and degree of neutropenia, abdominal computerized tomodensitometry (CT) documentation).

The unit chemotherapeutic protocol for patients with AML was HOVON, composed of cytarabine and idarubicine for the 1st induction, followed by cytarabine and daunorubicine for the 2nd induction. If the patient did not show a satisfactory hematological response after the first inductions, a salvage chemotherapy with clofarabine, fludarabine, cytarabine, G-CSF and idarubicin (FLAG-Ida) or cladribine, fludarabine, cytarabine, G-CSF and idarubicine (CLAG-Ida) was administrated. Other chemotherapeutic agents were used for patients with specific characteristics, such as azacytidine for very high-risk patients (age > 65 years, >30 % bone infiltration and in agranulocytosis when diagnosed), amsacrine for elderly, cardiac patients or combined with cytarabine in consolidation phases and hydroxacarbamine for palliative cases. Patients with lymphomas who were eligible for auto-transplant followed the BEAM protocol. Other protocols (non-BEAM) included high-dose

melphalan for patients with multiple myeloma or carmustine, etoposide and cytarabine (BEM) for relapse in elderly patients with lymphomas.

Definitions. NE was defined by the presence of all of the following criteria: (1) clinical signs or symptoms suggestive of abdominal infection (abdominal distention, tenderness and pain, diarrhea, vomiting and bloody stool), (2) neutropenic fever defined by an absolute neutropenic count (ANC) < 500 x, 10^6 cells/L), and a temperature > 38.0 (axillary) or 38.5 (rectal); (3) bowel wall thickening > 4 mm (transversal scan) over more than 30 mm (longitudinal scan) in any segment on abdominal CT, in the absence of an alternative diagnosis such as *Clostridium Difficile, Cytomegalovirus (CMV)* associated colitis, graft-versus-host disease (GVHD) or other abdominal syndroms. Patients who did not have a CT scan and those who had a CT scan showing lesions inconsistent with the aforementioned diagnosis were considered as non radiologically-proven NE.

Statistical analysis. Statistical analysis was performed using STATA version 15.1 software (StataCorp LP, College Station, Texas). Risk factors for NE were assessed by using univariate and multivariate regression models, significant risk factors with a P-value < 0.05 found on univariate analysis were further exposed to multivariate analysis. The normal data were reported in mean with standard deviation while the non-Gaussian data were reported as median with IQR..

Results

A total of 1223 neutropenic episodes occurred in 692 patients hospitalized during the study period (**Table 1**). The underlying malignancies were AML in 496 (41%) episodes, MM in 230 (19%), HL and NHL in 216 (18%), ALL in 136 (11%), MDS in 52 (4%) and other hematological malignancies (e.g. chronic leukemias or AA) in the remaining (93; 8%). Among AML patients, 276 (23%) were undergoing AML induction phases (HOVON) and 228 (19%) had a salvage regimen. In 444 (36%) HCT patients, 180 (15%) underwent the BEAM protocol and 264 (22%) followed non-BEAM protocols. The mean age was 52.1 years and the percentage of male was 61%. Of all co-morbidities, 10% were cardiac, 9% respiratory and 4% neurologic, 7% had diabetes, and 4% a chronic renal insufficiency.

A total of 72 episodes of NE (5.9%) occurred in 68 patients; the percentage of NE was 16.3% in AML induction, 5.6% in HCT using BEAM protocol, 4.8% in ALL induction, 2,9% in AML salvage and 1.9% in autologous HCT in a non-BEAM protocol (**Figure 1**).

In the HCT population, the single factor associated with NE was the BEAM protocol (OR = 3.40, CI 1.14-10.13, P = 0.028), compared to non-BEAM protocols**.**

In the AML population, we demonstrated a significant association between the development of NE and AML induction phases (OR = 4.0, CI 1.34-11.89, P = 0.01), amsacrine (OR = 2.800, CI 1.31-5-95, P = 0.008) and triple intra-thecal chemotherapy (OR = 2.1, CI 1.05-4-30, P = 0.04), compared to salvage chemotherapy (**Table 2**)**.**

Discussion

In this study, we provide a comprehensive overview of NE in a 10-year retrospective cohort of onco-hematological patients. Previous studies, mostly retrospective ones, have been limited by several factors, including heterogeneous groups of patients at risk and/or failure to use specific radiological criteria (2, 10), and/or a very limited number of cases (only one study included >50 cases of NE, but only half of them did have a radiologically-proven NE, 26). Prospective studies are also limited to only a few cases of the disease (maximum 25 cases of NE; 8-10, 11, 27). Thus, to our knowledge, this is the largest study of NE adult patients with a homogenous and reliable radiological diagnosis criteria of bowel wall thickening on CT, and the only allowing for differential incidence estimates according to the underlying disease and chemotherapy regimens.

Overall, we demonstrated an incidence of NE of 5.9% in our population at risk (patients hospitalized for hematological malignancies, for high-dose chemotherapy in solid tumor or for aplastic anemia), which is consistent with the incidence reported in a large review of 21 studies (5.6%, 10). Other studies described incidences varying from 3.5 to 6.5% in sample sizes never exceeding more than 500 neutropenic episodes (9, 23, 29, 31). We demonstrated that the incidence of NE is very different when the radiological criterion is accounted for, emphasizing the importance of radiological confirmation for the diagnostic of NE.

Our study clearly illustrates important differences according to the chemotherapy regimens, ranging from 16.3% among patients receiving an induction with a 7+3 (i.e HOVON) based therapy to only 1.9% in patients receiving non-BEAM chemotherapy previous HCT. Among patients undergoing induction chemotherapy for AML, the

incidence of NE was 16.3% for those undergoing a 7+3 regimen compared to only 2.9% in salvage regimen. Other studies described different incidences of NE, varying from 2.35% to 15.4% in the acute leukemia population either without lymphoid vs myeloid distinction, without any radiological diagnostic criterion of NE or with smaller sample sizes (9, 10, 23, 24, 27, 29, 30).

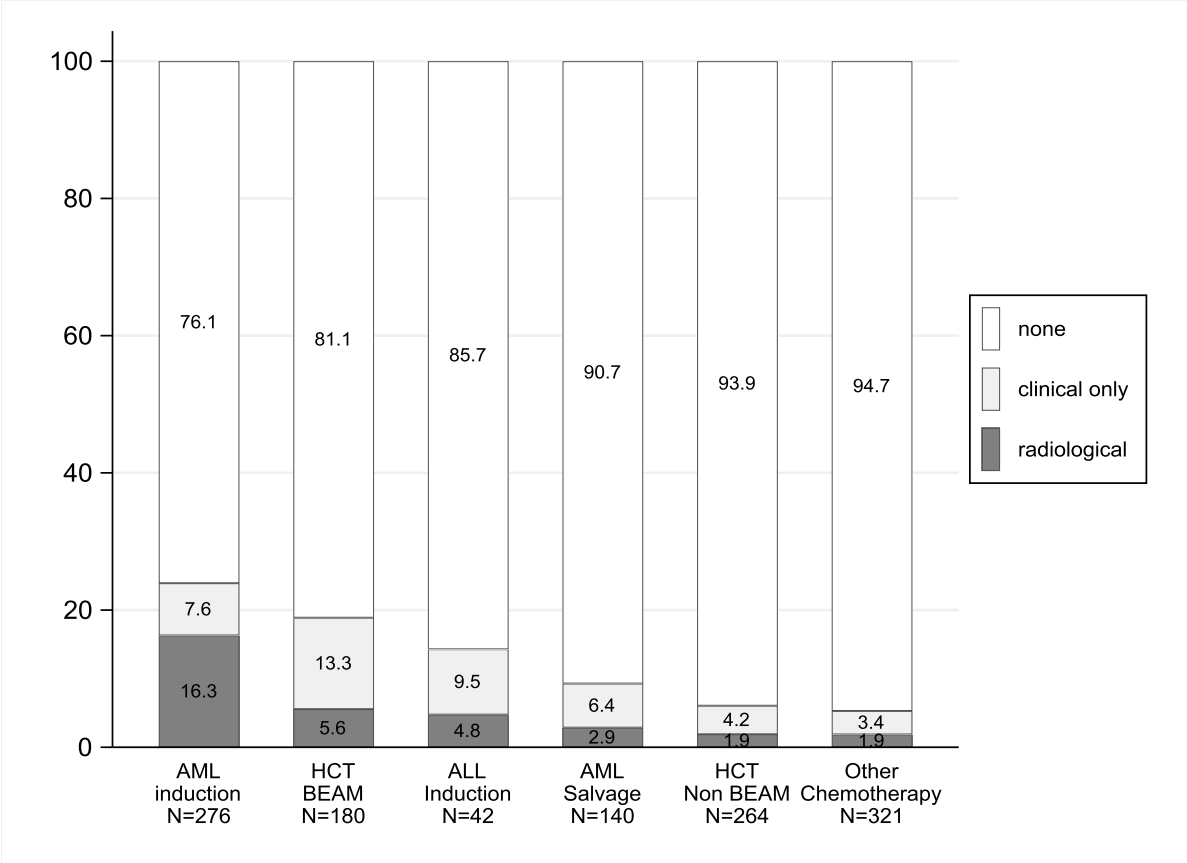
Among patients undergoing autologous HCT, the incidence of NE was 5.6% for those undergoing BEAM regimen compared to only 1.9% for those under other protocols. Gil et al. reported an incidence of NE proven by abdominal US of 12% among BEAM patients, in a smaller population (N=297) but with more NE cases (N=32) (3). Both studies differed by the number of Hodgkin lymphomas (89 in the Gil and al study versus 29 patients in our study). This higher number of NE cases may be explained by the nature of the Gil and al study, which may have increase the number of NE diagnoses by using abdominal US. This is the first study to analyze and confirm BEAM as a NE risk factor in HCT population with a CT scan criterion.

Ara-C alone, which plays an important part in the immunosuppression in the protocol, had already been described without analysis clarification of chemotherapeutic regimens or dosis use (5, 6, 9, 34). Unexpectedly, the incidence of NE was dramatically higher among acute leukemia patients receiving the “7+3” protocol (16.3%) compared to those receiving FLAG/CLAG salvage (OR = 4.0, CI 1.34-11.89, P = 0.01). The difference between these two groups might be a consequence of the immunomodulator effect of fludarabine or cladribine, given 4 hours before cytarabine infusion, and could be a key in decreasing the inflammatory state of hemato-oncological patients. Another impact could be the systematical concomitant use of G-CSF in the salvage regimen, which decreases the entry in agranulocytosis.

As for the other risk factors, azacitidine is a regimen used in selected high-risk patients that can be prone to NE because of their long hospitalizations. Triple intra-thecal chemotherapy has probably not a direct effect on NE but could reflect the patients with extensive diseases such as those with neurological spread, poorer prognosis after genetic risk classification, hyperleucocytosis, rapid agranulocytose or uncontrolled cancers that might infiltrate the abdominal layers and be part of the pathogenesis of NE. As the pathogenesis of its implication is not yet well-understood and no statistical analysis has been done on the subject, further investigations of its risks are to be emphasized in the future.

In conclusion, this is a retrospective study made among hemato-oncological patients who developed radiologically-confirmed NE, estimating reliable estimates of NE in different populations and demonstrating the BEAM and the HOVON protocols as two main risk factors of developing the disease. Prospectively, this could help identify high-risk groups in the onco-hematological population for an early clinical and radiological recognition of NE, as well as adapt strategic prevention, such as oral specific prophylactic antibacterial and/or antifungal therapy, combined with early give of G-CSF. The consideration of genetic risk classification is to emphasize further in the future and could lead to individualized chemotherapeutic treatments, causing less secondary adverse effect of the regimens without reducing their efficacy.

Figure 1. Percentage of patients with clinical manifestations suggesting of neutropenic enterocolitis and those with radiologically-proven neutropenic enterocolitis according to the type of chemotherapy at the isolation Unit of CHUV (2007-2017).



Note: AML: acute myeloid leukemia, HCT: autologous hematopoietic cell transplant, ALL: acute lymphoblastic leukemia, BEAM chemotherapy comprises administration of BCNU, etoposide, ARA-C, and melphalan; non-BEAM regimen include melphalan (N=223) or other regimen (N=41); salvage regimen include fludarabine, cladribine or clofarabine with high dose cytarabine, each administered with granulocyte colony stimulating factor (G-CSF) +/- idarubicine. Other chemotherapy regimens include those administered for lymphoma, myeloma as well as consolidation courses for AML and ALL.

Table 1 : Demographic characteristic of the population

Variable	All episodes N= 1223 N (%)	NE episodes N = 72 N (%)	NE in AML N = 41 N (%)	NE in HCT N = 15 N (%)
Age at cohort entry (mea years; range)	52 (18-75)	54 (18-75)	52 (29-75)	58 (37-68)
Male sex	746 (61)	43 (60)	25 (61)	9 (60)
Ethnictiy				
Caucasian	1142 (93)	69 (96)	40 (98)	13 (87)
African	42 (3)	2 (3)		2 (13)
Asian	19 (2)			
South American	17 (1)	1 (1)	1 (2)	
Underlying disease				
AML	548 (45)	45 (63)	41 (100)	2 (13)
MM	230 (19)	3 (4)		3 (20)
NHL/HL	216 (18)	11 (14)		9 (60)
ALL	136 (11)	4 (6)		
Other [1]	93 (8)	9 (13)		1 (7)
Comorbidities				
Cardiac	124 (9)	10 (14)	4 (10)	28 (8)
Respiratory	110 (9)	4 (5)	3 (7)	23 (6)
Diabetes	82 (7)	4 (5)	1 (2)	26 (7)
Chronic renal failure	52 (4)	2 (3)		20 (6)
Neurological	53 (4)	3 (4)	2 (5)	13 (4)
Chemotherapeutic regimens				
HOVON-induction	276 (23)	45 (63)	37 (90)	
AML Salvage	228 (19)	6 (8)	4 (10)	
HCT BEAM	180 (15)	10 (14)		10 (67)
HCT non-BEAM	264 (22)	5 (7)		5 (33)
Other chemotherapies[2]	275 (22)	4 (8)		

Note : AML: acute myeloid leukemia ; MM: multiple myeloma; NHL: non-Hodgkin lymphoma; ALL : acute lymphoblastic leukemia; MDS: myelodysplastic syndrome; HL : Hodgkin lymphoma; NHL : Non-Hodgkin lymphoma; HCT : hematopoietic cell transplantation; HOVON include cytarabine and idarubicine/daunorubicine ; Salvage regimen include fludarabine, cladribine or clofarabine, high dose Ara-C, each administered with granulocyte colony stimulating factor (G-CSF) +/- idarubicine; HCT BEAM include BCNU, etoposide, ARA-C, and melphalan; non-BEAM regimen include melphalan or other chemotherapies.

[1] Other underlying diseases include aplastic anemia (N=6), chronic myeloid (N=28) and lymphoid (N=3) leukemia and others such as solid tumors (N= 56)

[2] Other chemotherapies include those administrated for MM or HL/NHL, ALL inductions or consolidation regimens

Table 2. Multivariate analysis of neutropenic enterocolitis episodes in acute myeloid leukemia patients

	Multivariate N=41	
Risk factors	**OR (95%CI)**	**P-value**
Chemotherapy		
Azacitidine	3.960 (0.96-16-38)	**0.058**
Amsacrine	2.800 (1.31-5-95)	**0.008**
Intra-thecal Cytarabine	2.120 (1.05-4-30)	**0.036**
HOVON induction	4.000 (1.34-11-89)	**0.013**

Note : HOVON include cytarabine and idarubicine or daunorubicine

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