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MAJOR ARTICLE

Epidemiology, Risk Factors and Outcome of Neutropenic Enterocolitis in Onco-Hematological Patients according to Chemotherapy Regimen

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Background. While neutropenic enterocolitis (NEC) is a well-known life-threatening complication during intensive chemotherapy, its incidence, impact and outcome on specific at-risk populations remain ill-defined.

Methods. We report 178 NEC episodes during 1963 myeloablative chemotherapy courses among 1259 adult patients with acute myeloid (AML) or lymphoid (ALL) leukemia or receiving

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autologous hematopoietic stem cell-transplant (auto-HCT) for lymphoma or multiple myeloma. Risk factors were assessed by multivariate logistic regression models.

Results. Most NEC cases (93.3%) occurred during AML induction (N=92, 13.8% of chemotherapy course) and auto-HCT (N=74, 9.5%). Independent risk factors for NEC during AML induction included high-dose corticosteroids (OR=2.07, 95%CI 1.29-3.30, P=0.002), elevated circulating blasts at the time of diagnosis (>50 G/L, OR=2.02, 95%CI 1.15-3.56, P=0.02) and use of azacitidine (OR=2.45, 95%CI 1.01-5.90, P=0.05); purine-based regimens (e.g. FLAG-Ida) was an independent protective factor (OR=0.27, 95%CI 0.15-0.47, P<0.001). Independent risk factors after auto-HCT included BEAM versus another conditioning protocol (OR=3.28; 95%CI 1.98-5.43, P<0.001) and age (OR=1.03 per year, 95%CI 1.01-1.06, P=0.007). For both AML induction and auto-HCT, NEC was associated with longer hospitalization (P=0.03 and P<0.001), sepsis (quick SOFA≥2, P=0.03 and P<0.001), fungemia (P<0.001 and P=0.01) and intensive care admission (P=0.03 and P<0.001, respectively). NEC was associated with increased in-hospital mortality during AML induction (6.5% versus 2.4%, P=0.04) but not during auto-HCT (P=0.3).

Conclusions. The incidence of NEC depended on chemotherapeutic regimens, with higher occurrence during standard "7+3" AML induction and BEAM conditioning for auto-HCT. NEC was associated with longer hospitalization and increased morbidity, but 30-day mortality was lower than previously reported.

Keywords: neutropenic enterocolitis; chemotherapy; hematological malignancies;

INTRODUCTION

Neutropenic enterocolitis (NEC) is known as a life-threatening, necrotizing bowel inflammation occurring primarily in neutropenic patients undergoing intensive chemotherapy for the treatment of hematological malignancies [1,2]. Pathophysiological events leading to NEC result from the combined action of chemotherapy-induced mucosal damage, coagulation disorders and profound neutropenia, promoting bacterial and fungal translocation of the resident flora [2,3].

The clinical manifestations of NEC overlap with those seen in other abdominal conditions, such as colitis due to *Clostridioïdes difficile,* cytomegalovirus (CMV) or ischemia, appendicitis, Ogilvie syndrome or gastrointestinal graft-versus-host disease (GvHD) [2,4]. The increasing use of computed tomography (CT) has improved our ability to distinguish NEC from the other digestive syndromes. Current diagnostic criteria proposed by Gorschlüter et al. [5] include an absolute neutrophil count (ANC) <500 x 10^6 cells/L, fever >38.3°, and bowel wall thickening (BWT) >4mm with a bowel length >30 mm detected by abdominal ultrasound (US) or CT, in the absence of any other cause. The 4mm cutoff is considered reliable as it is very rare in non-inflammatory bowel disease after chemotherapy.

In the absence of a clear definition, the epidemiology of NEC has remained ill-defined, with reported incidence ranging from 6% to 46% [2,5–8]. Recent cytotoxic chemotherapy is the most reported risk factors [2,9]. Preexisting bowel abnormalities and prior episodes of NEC appear to increase the risk of relapse [2]. Altogether, patients' heterogeneity and absence of multivariate models in most studies makes it difficult to determine which factor are independently associated with NEC.

The management of NEC relies mainly on expert's opinion [5]. Medical treatment usually combines broad-spectrum antibiotics active against gram-negative bacteria and anaerobes [10], supportive therapy (bowel rest, intravenous fluids, parenteral nutrition) and granulocyte colony-stimulating factor (G-CSF); the benefit of empirical antifungal therapy in non-critically ill neutropenic patients with NEC is not clearly established [10]. While surgery was initially considered for all cases [11,12], its current use is controversial [13,14]. Mortality rate is high, ranging from 10 to 63% [3,5,7,15–19]. The goals of this study were to determine the incidence, outcome and risk factors of NEC in a cohort of prospectively collected onco-hematological patients.

METHODS

This study was conducted in a prospectively collected cohort of ≥18-year-old patients with hematological malignancies hospitalized within the isolation Unit of Lausanne University Hospital between January 1st, 2007 and December 31, 2023 (MINCO registry). It was approved by the local Ethics Committee (Swissethics 2017-01975).

Definitions

Patients with acute myeloid leukemia (AML) or myelodysplastic syndrome with increased blasts 2 (MDS-IB2) were treated with cytarabine plus anthracycline induction according to the standard arm in ongoing HOVON/SAKK trials [20] or purine-based chemotherapy (FLAG-ida, CLAG-ida) [21–25] (supplementary Table 1). Patients with acute lymphoblastic leukemia (ALL) were treated according to ongoing GRALL protocols [26]. Conditioning chemotherapy regimens for auto-HCT were stratified as "BEAM protocol" for patients with lymphoma [15], and "other conditioning regimens", including melphalan for multiple myeloma (MM), carmustine and thiotepa for central nervous system lymphoma, and busulfan and cyclophosphamide for AML patients [15]. Allogenic HCT is not performed in this hospital.

Febrile neutropenia (FN) was defined by the presence of an ANC <500 cells/mm^3 and a tympanic temperature of ≥38.5°C or of ≥38.0°C measured twice over a 2-hours period. During each episode, the investigations systematically included sets of blood cultures, cultures from urine and any suspected site of infection, and a chest X-ray. Stool cultures to check for *Salmonella*, *Shigella* or *Campylobacter* species and testing for *C. difficile* toxins were routinely performed in cases of

diarrhea, as well as CMV testing in patients with relapsed acute leukemia patients and a history of allogeneic HCT. Broad-spectrum empiric antibiotic therapy (cefepime +/- metronidazole or piperacillin-tazobactam) is promptly started after microbiological sampling at each episode of febrile neutropenia. Antifungal prophylaxis during neutropenia was prescribed according to international recommendations [10,27].

Data collection

Data were extracted from the MINCO registry implemented in SECUTRIAL®, which contains an extensive range of prospectively collected data, including demographics, duration of neutropenia, characteristics of infections, treatments, outcomes, sequential Sepsis-related Organ Failure Assessment (SOFA) and quick SOFA (qSOFA) scores [28]. All data were systematically collected by trained study nurses in a dedicated case-report form, reviewed by senior ID physicians and classified as microbiologically documented infection (MDI), clinically documented infection (CDI) or fever of unknown origin (FUO). Prognosis for AML was described according to of the 2017 European Leukemia Network genetic categories [29]. Death occurring after hospitalization was obtained from the official death registry. The analyses were performed by chemotherapy cycles (each corresponding to a single chemotherapy and neutropenia episode), as the main risk conditions change at each cycle. The total dose of corticosteroids received during chemotherapy episode is calculated in mg of prednisone equivalent [30].

The diagnosis of NEC was established when patients with febrile neutropenia had clinical signs and/or symptoms suggestive of abdominal infection (abdominal distension, tenderness and pain, diarrhea, vomiting and/or bloody stools), with the presence of BWT >4mm (measured on axial CT images) over more than 30mm of length (measured on coronal CT images) in any bowel segment, as proposed by Gorschlüter et al. [5], in the absence of other well-recognized entities on CT (appendicitis, diverticulitis, cholecystitis, cholangitis, GvHD, ischemic colitis) or alternative diagnoses including enteric pathogens (such as *C. difficile* and *CMV*-associated colitis). All abdominal CT examinations were reviewed by a radiologist with >20 years of practical experience in gastrointestinal imaging. The presence or absence of NEC was sought in the 4 quadrants of the small bowel (right upper, left upper, right low, left low) and the different segments of colon (caecum, ascending colon, transverse colon, descending colon, sigmoid, rectum). The maximal wall thickness for each segment and the percentage of involvement of the analysed bowel segment were measured. Episodes of NEC occurring within 10 days of *C. difficile* colitis were excluded.

Statistical analysis

Statistical analysis was performed using Stata® version 18.0 software (College Station, Texas). Risk factors of developing NEC were assessed in homogeneous groups of patients by using univariate and multivariate logistic regression models. Factors that were or tended to be associated with the endpoint on univariate analysis were entered into multivariate analysis and selected by using backward stepwise regression. Kaplan-Meier survival analyses were performed using the

STS graph function with a landmark approach. Statistical difference was considered significant for a p-value <0.05.

RESULTS

Study population

A total of 1963 chemotherapy courses were analyzed in 1259 patients (Table 1). Median patients' age was 58 years (interquartile range 17) and 60.0% were men. Most frequent malignancies were AML and MDS-IB2 (N=379, 30.1%), multiple myeloma (MM, N=374, 29.7%), lymphoma (N=351, 27.9%) and ALL (N=80, 6.4%). Of the 1963 chemotherapy courses, 665 were for the treatment of AML ("AML population", including 231 first and 180 second standard inductions and 254 purine-based inductions or salvage) and 776 were conditioning regimen for auto-HCT ("auto-HCT population", including 289 with a BEAM and 487 with another conditioning protocol, e.g. melphalan). The other chemotherapy episodes included 47 ALL inductions and 475 chemotherapies for other hematological malignancies (detailed in supplementary Table 2).

Characteristics of Neutropenic Enterocolitis

A total of 178 episodes of NEC were diagnosed during 1963 courses of chemotherapy (9.1%) (Supplementary Table 3). The vast majority (93.3% of NEC episodes) occurred in the AML (N=92, 13.8% of courses) and the auto-HCT populations (N=74, 9.5%). Yet, the incidence of NEC varied within these two groups after stratification according to specific chemotherapeutic regimen (Figure 1). In the AML population, this incidence was much higher during induction with a standard ("7+3") protocol (18.6% for 1st and 17.8% for 2nd induction) than during purine-based chemotherapy (6.7%). In the auto-HCT population, it was higher among patients receiving a BEAM protocol (15.2%) compared to those receiving another protocol (6.2%). The incidence of NEC was 8.5% during ALL induction and only 1.7% during other chemotherapies.

The analysis of abdominal CT examinations revealed that NEC involved more than one intestinal segment in 91% of cases (median number of segments=3, interquartile range [IQR]=3), with the small intestine situated in the upper left abdominal quadrant (50.0% of cases) and the ascending colon (48.9%) being the most frequently affected localizations (Figure 2). The median maximal bowel wall thickening ranged from 8 mm (IQR=3) in the right lower quadrant of the small intestine to 15 mm (IQR=8) in the caecum.

Risk factors

In the AML population, independent risk factors for NEC included high-dose corticosteroids (>100 mg prednisone equivalent, OR=2.07, 95%CI 1.29-3.30, P=0.002), elevated circulating blast count at the time of AML diagnosis (>50 G/L, OR=2.02, 95%CI 1.15-3.56, P=0.02, Table 2) and concomitant use of azacitidine, a pyrimidine analogue (OR=2.45, 95%CI 1.01-5.90, P=0.05).

Purine-based chemotherapy instead of standard induction was an independent protective factor (OR=0.27, 95%CI 0.15-0.47, P<0.001). Additional risk factors emerged when the analyses were further limited to patients receiving standard AML induction, the group with the highest incidence of NEC, by entering specific regimens into the multivariate models (Table 3). In addition to high-dose corticosteroids (prednisone equivalent >100 mg, OR=2.77, 95%CI 1.57-4.88, P<0.001), elevated circulating blast counts (OR=2.64, 95%CI 1.37-5.08, P=0.004 for blasts 20-50 G/L; OR=2.25, 95%CI 1.08-4.69, P=0.03 for blasts >50 G/L, compared to blasts <20 G/L) and the use of azacitidine (OR=3.29, 95%CI 1.03-10.5, P=0.04), the analysis also identified a previous NEC (OR=3.65, 95%CI 1.48-9.04, P=0.005), as well as the use of regimens containing idarubicin (OR=2.66, 95%CI 1.31-5.41, P=0.007) and amsacrine (OR=3.24, 95%CI 1.54-6.84, P=0.002), versus ARA-C alone or in combination with daunorubicin, as independent risk factors for NEC.

In the auto-HCT population, the only two factors independently associated with NEC were conditioning with BEAM protocol (OR=3.28; 95%CI 1.98-5.43, P<0.001, Table 4) versus other regimen and increasing age (OR=1.03 per year, 95%CI 1.01-1.06, P=0.007). In the ALL population, no significant risk factor for NEC was identified, but the number of such episodes was quite small (N=4, supplementary Table 4). In the other chemotherapies, the only independent risk factor for NEC was previous NEC (OR=5.76, 95%CI 1.08-30.73, P<0.001, supplementary Table 5) despite the small number of NEC cases (N=8).

Treatment and outcome

Broad spectrum antibiotics were administered to all NEC cases (100%), as an initial empirical therapy in 99 cases in whom NEC appeared as the first episode of neutropenic fever (55.6%), or as a switch from (N=84, 47.2%), or continuation of (N=15, 8.4%), ongoing antibiotics, when NEC was preceded by one or several episode(s) of neutropenic fever (Supplementary Table 3). Antifungals were administered in 119 out of 178 cases of NEC (66.9%), as an initial antifungal therapy (N=49, 27.6%), or as a switch from (N=18, 10.1%), or maintenance of (N=52, 29.2%), antifungals previously given as a prophylaxis or a treatment. Abdominal surgery with resection was performed in 3 episodes of NEC, only one of whom had perforation.

Neutropenic episodes complicated by NEC compared to those without NEC were characterized by a longer hospitalization (median 34 days [IQR=25] versus 32 [IQR=17], P=0.03 for AML induction, median 26 days [IQR=8], versus 20 [IQR=6], P<0.001 for auto-HCT, Table 5), a higher occurrence of sepsis (quick SOFA≥2 19.6% versus 11.3%, P=0.03 for AML induction; 23.0% versus 5.4%, P<0.001 for auto-HCT; SOFA>10 4.3% versus 1.0% for AML induction, P=0.03; 4.1% versus 0.4%, P=0.003 for auto-HCT) and a higher need for transfer to the intensive care unit (ICU) (14.1% versus 7.3%, P=0.03 for AML induction; 18.9% versus 2.1% P<0.001 for auto-HCT). NEC was associated with a higher rate of fungemia (6.5% versus 0.7%, P<0.001 during AML induction; 4.1% versus 0.6%, P=0.01 during auto-HCT), and, during AML induction but not auto-HCT and a higher rate of bacteremia due to gram-positive cocci (38.0% versus 25.7%, P=0.01). Finally, NEC was associated with a higher rate of in-hospital mortality during AML

induction (6.5% versus 2.4%, P=0.04), particularly after purine-based chemotherapy (17.6% versus 2.5%, P=0.005; supplementary Table 6), but not during auto-HCT (P=0.3). However, overall, long term survival was not affected by NEC (log rank test, P=0.7 for AML and P=0.5 for auto-HCT, Figure 3).

DISCUSSION

Although NEC is considered as a life-threatening condition, its exact incidence and outcome have long remained undefined, probably due to the lack of a standard definition, inhomogeneity and limited size of study populations and retrospective nature of most reports [2,5]. To our knowledge, this is the largest NEC cohort study and the first to stratify risk factors analyses by chemotherapeutic regimen.

Historically, NEC was associated with the use of cytarabine [6,7,9] which induces mucosal damages in the gastro-intestinal tract [31]. Yet, this observation is not useful for predicting which AML patients are likely to develop NEC, since this drug is part of virtually all regimen used for AML induction [6,7,9]. We show for the first time that the incidence for NEC can greatly vary among patients receiving cytarabine. The incidence of NEC was quite elevated after both a first (18.6%) and a second (17.8%) induction with a standard ("7+3") regimen, while cytarabine doses greatly differ among these protocols (200mg/m^2/day D1-D7 versus 2000mg/m^2/day D1-D6, respectively). Furthermore, purine-based therapy (regardless of its use as front line or salvage therapy) was associated with a lower rate of NEC compared to standard "7+3" induction despite elevated doses of ARA-C (2000mg/m^2/day D1-D5 for FLAG). This suggests that cytarabine bowel toxicity may not much rely on its dosage, but rather on factors such as the number of days it is administered, its daily infusion mode (1 versus 2 times per day, long versus short administration) and/or the type of associated chemotherapeutic drug. In standard AML induction, the incidence of NEC was higher when cytarabine was combined with idarubicin, a semi-synthetic glycoside analogue of daunorubicin with slightly different pharmacokinetic properties, or amsacrine compared to cytarabine alone or combined with daunorubicin, suggesting a potentiating role for these drugs, as previously reported with amsacrine [32]. The use of upfront G-CSF, which is systematic in purine-based regimen (e.g. FLAG-Ida) may have contributed to reduce neutropenia duration and the risk for NEC in this group. Nevertheless, G-CSF was not a significant protective factor for NEC during standard AML induction. The other relevant risk factor for NECs in our AML population was a previous NEC and the high level of circulating blasts (> 50 G/L) at admission. A likely mechanism is the presence is leukemic infiltration of the bowel at the beginning of chemotherapy, plays a role in the pathogenesis of NEC, as previously suggested [3], although this has not been confirmed histologically [33].

The second regimen associated with NECs was auto-HCT conditioning with a BEAM protocol, with a global incidence of 15% (16% for NHL and 13% for HD); this is consistent with a smaller report of 25 episodes of NEC occurring in 179 BEAM recipients (14%), although the proportion

of NEC differed according to the underlying disease in this study (19% for NHL and 9% for HD) [15]. In a recent prospective study of 129 lymphoma patients conditioned with BEAM, NEC incidence was even higher (31%), but the diagnosis was obtained by ultrasonography, a technique that is more subjective and far less reproducible than CT [34]. Since the doses of melphalan and cytarabine are lower in the BEAM protocol than in the conditioning regimen for MM and purine-based AML regimens, respectively, NEC may result from a potentiating effect of the other drugs used in these regimens, namely carmustine and etoposide.

This study is the first to identify steroids as a risk factor for NEC. Cumulative doses >100mg prednisone equivalent significantly increased this risk during AML induction, and higher doses (>250 mg) also tended to do so during auto-HCT. A smaller study of 52 episodes of typhlitis failed to detect such an association, but the results are difficult to interpret in the absence of dose reporting [9]. Since steroids are increasingly administered within or in addition to chemotherapy regimen to prevent gastro-intestinal side effects, to treat severe cutaneous and/or digestive damage secondary to high doses of cytarabine, the identification of their role as a risk factor for NEC is clinically relevant.

While earlier studies reported NEC mortality rates >50% [5,7], 30-day mortality rates ranged from 9% to 30% in more recent reports [3,15–18,35]. In-hospital mortality (6.5% for AML induction and 2.4% for auto-HCT) was even lower in our study. Such differences may be due by several factors. First, the literature is often limited to case reports or small case series, with a potential publication bias towards severe cases [5,35,36]. Second, clinical screening, diagnostic procedures and criteria definition for NEC have evolved and differ among centers, making it difficult to compare NEC incidence and mortality rates. Finally, close monitoring since the first sepsis signs, as illustrated by our high ICU transfer rate, and prompt management of septic shock [37], may have contributed to limit mortality [2,33,38]. In rare cases, NEC was associated with severe infections, such as candidemia, with high mortality [36].

A conservative management has become the standard to care in most institutions [35]. Our data confirm the efficacy of conservative approach, including broad-spectrum empiric antimicrobial therapy promptly started at the onset of fever [10] and general supportive care. Surgical management was reserved for the situations of clinical deterioration despite optimal medical treatment as proposed by Shamberger et al [14]. Indeed, a recent meta-analysis still favors surgery for patients with severe NEC requiring intensive care management [13].

This study has limitations, including its retrospective design and the fact that CT examinations was decided by the treating physician. However, all patients were prospectively included, and data systematically reported in real time. In auto-HCT patients, physicians may have been less prone to perform CT-scan, as neutropenia is short, and NEC usually diagnosed just before neutrophil recovery. This may have contributed to underestimate the incidence of NEC in patients with auto-HCT with BEAM conditioning (14%), compared to the incidence observed in another study (31%), in which abdominal ultrasonography was performed systematically [34].

In conclusion, NEC is a common complication in neutropenic patients receiving standard AML induction chemotherapy or BEAM conditioning for auto-HCT. It requires close monitoring and abdominal CT examination in these groups, particularly in AML patients with elevated circulating blast counts at diagnosis, high dose corticosteroids and/or previous NEC. Our results emphasize the effectiveness of medical management with a low day-30 mortality and the absence of direct impact on long-term survival.

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Authorship Contributions: PYB, CS and ASB designed the study. CS collected specific NEC data, SA and MG collected specific hematological data. ASB designed the full clinical database under the supervision of PYB, with the contribution of OM for the period 2007-2014. MF drew up the treatment plans and validated the pharmacotherapy analyses. SSK and KM reviewed all abdominal CT examinations. PYB and ASB performed statistical analyses. PYB, ASB, CS, MG, MF and OS contributed to the interpretation of the data. ASB, PYB and CS drafted the original manuscript. All authors revised and approved the final version of the manuscript.

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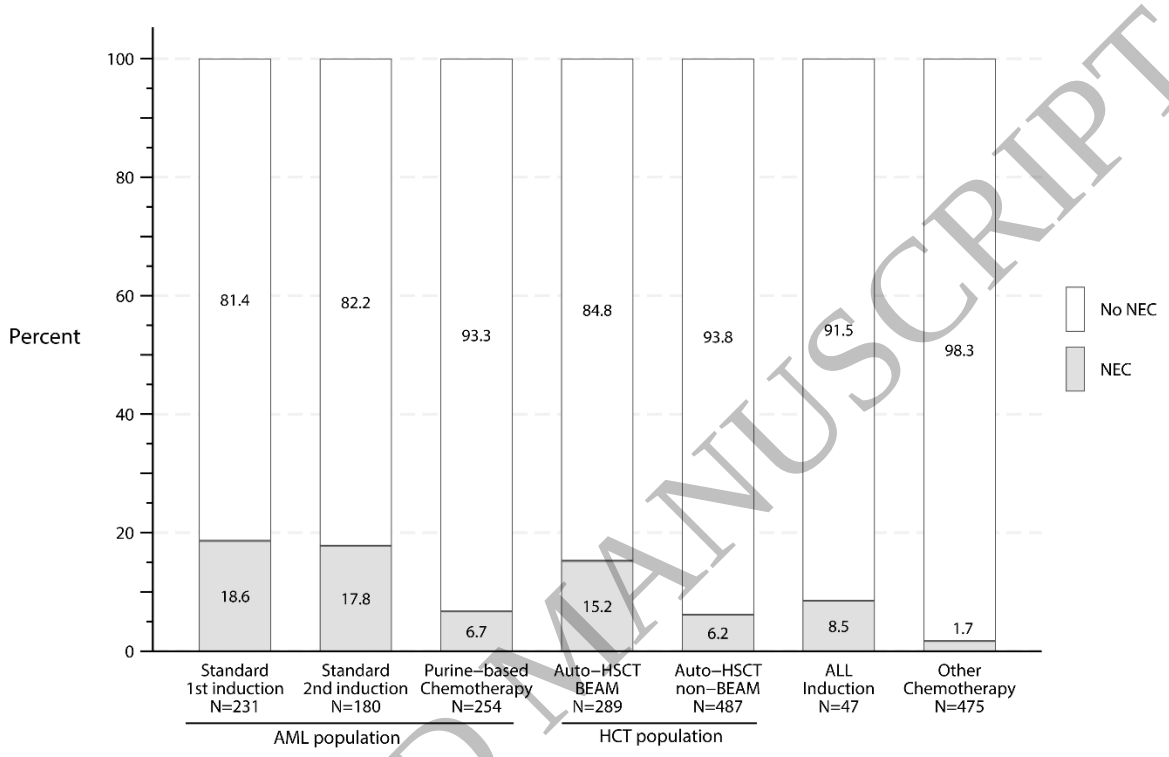
FIGURES' LEGENDS

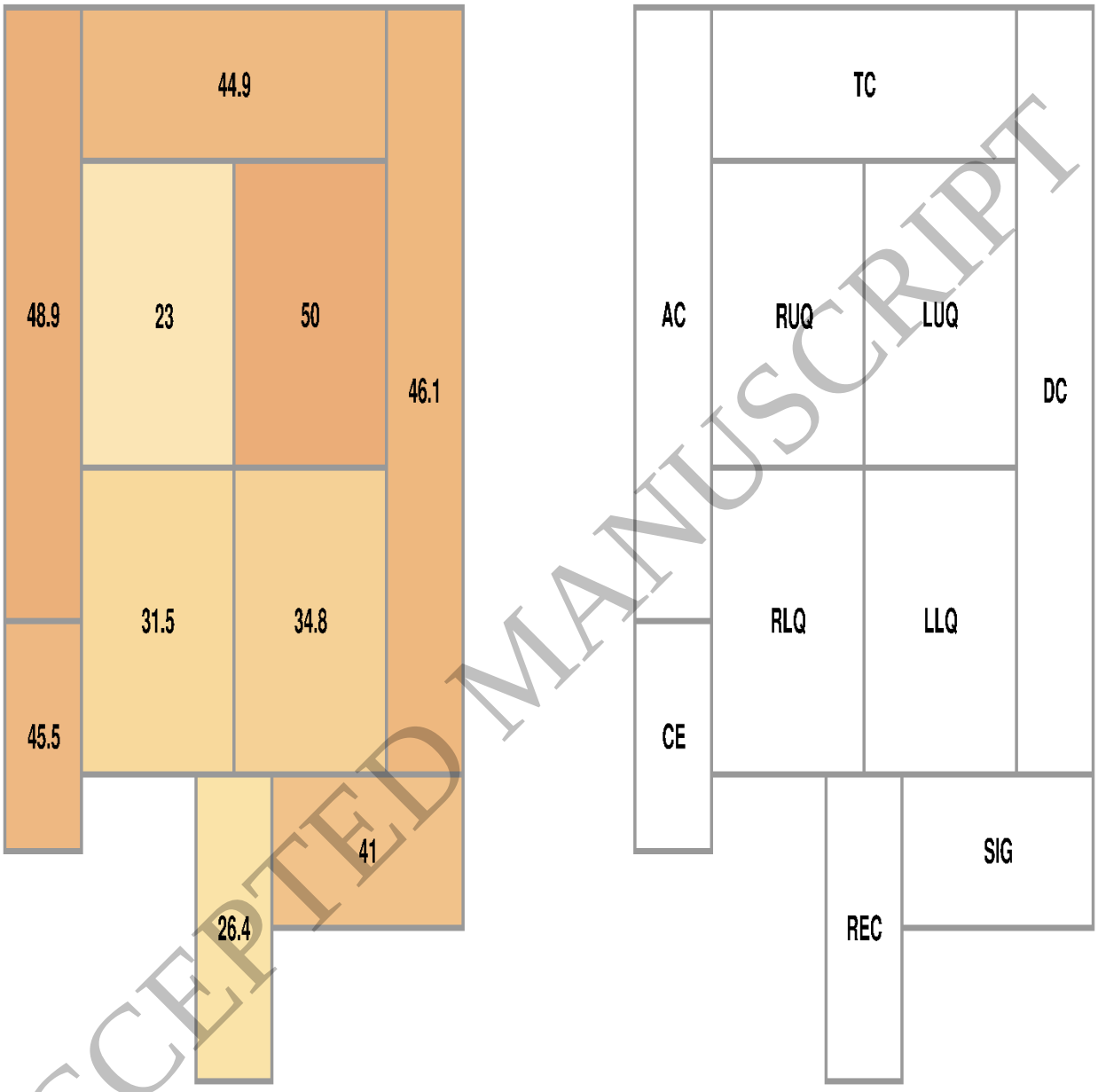
Figure 1. Incidence of neutropenic enterocolitis in onco-hematological patients according to different chemotherapy regimens.



Neutropenic enterocolitis (NEC) was defined by the presence of clinical signs and/or symptoms suggestive of abdominal infection, in the absence of an alternative diagnosis, and a bowel wall thickening > 4 mm (measured on axial CT images) in any bowel segment

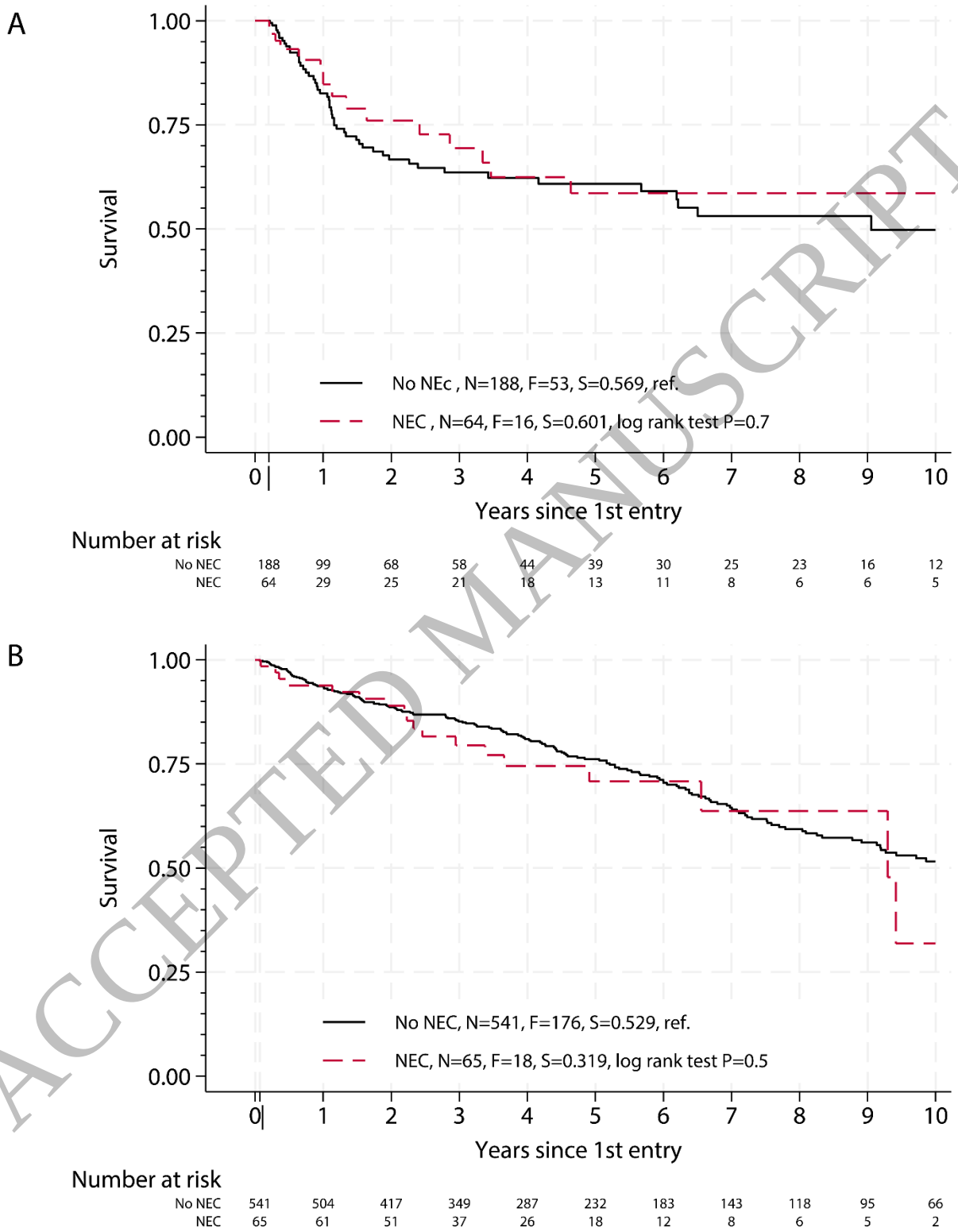
ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; Auto-HCT: autologous hematopoietic cell transplant; BEAM: carmustine, etoposide, cytarabine and melphalan; NEC: neutropenic enterocolitis.

Figure 2. Anatomic localization of neutropenic enterocolitis in onco-hematological patients.



Values within the different segments represent the percentage of NEC patients for whom a wall thickening > 4 mm was measured on axial CT images. AC: ascendent colon; CE: caecum; DC: descendent colon; LLQ: left lower abdominal quadrant; LUQ left upper abdominal quadrant, RLQ : right lower abdominal quadrant; RUQ: right upper abdominal quadrant; SIG: sigmoid; TC: transverse colon; REC: rectum.

Figure 3. Overall survival analysis in hematological patients according to the presence or absence of neutropenic enterocolitis.



DOI: 10.1093/cid/ciaf134

We used a landmark analysis to estimate overall survival according to NEC, starting 10 weeks after the 1st AML induction (Panel A) and 3 weeks after auto-HCT conditionning (Panel B), with censoring when patients were hospitalised for a novel treatment making them again at risk to develop NEC, including induction for new (after auto-HCT) or relapsed AML, auto-HCT (following AML induction or after a previous auto-HCT) or allo-HCT. The 3 and 10 weeks cut-offs (indicated by an arrow) were chosen since all NEC had occurred within 3 weeks after auto-HCT conditionning and within 10 weeks after the 1st AML induction (a duration encompassing neutropenic episodes of both the 1st and 2nd induction), respectively. Long term survival was assessable in 606 patients with auto-HCT and 252 patients with AML induction. N stands for number at risk, F for failure (death) and S for survival.

Alt Text

Figure 1. Graph showing columns corresponding to the percentage of patients with and without neutropenic enterocolitis according to the type of chemotherapeutic regimen. The total number of patients in each group is provided at the bottom of each column.

Figure 2. Graph showing the localisation of neutropenic enterocolitis in onco-hematological patients. The left panel depicts different anatomical regions of the bowel filled with colors densities corresponding to the occurrence of enterocolitis. The right panel shows the same regions labelled with their anatomical names.

Figure 3. Graph showing Kaplan-Meier survival curves of patients with or without neutropenic enterocolitis over 10 years. The upper panel stands for patients with acute myeloid leukemia and the lower panel for patients with autologous hematolopoïetic cell transplantation. Statistics for the comparison between groups and number of patients at risk for each year are shown at the bottom of each panel.

Table 1. Characteristics of the study population.

	All population		Chemotherapy for AML		Autologous HCT	
Characteristics[a]	**N**	**%**	**N**	**%**	**N**	**%**
Number of chemotherapy courses	1963		665		776	
Number of patients	1259		324		726	
Patients demographics[b]						
Median age (IQR)	58	(17)	57	(18)	57	(14)
Gender, Male	755	(60.0)	193	(59.6)	439	(60.5)
Ethnic, Caucasian	1159	(92.1)	311	(96.0)	654	(90.1)
Chronic health conditions[b]						
Cardiac insufficiency	124	(9.8)	37	(11.4)	70	(9.6)
Pulmonary disease	103	(8.2)	32	(9.9)	61	(8.4)
Diabetes mellitus	106	(8.4)	18	(5.6)	62	(8.5)
Neurologic disease	72	(5.7)	14	(4.3)	36	(5.0)
Chronic renal insufficiency	65	(5.2)	10	(3.1)	42	(5.8)
Underlying malignancy[b]						
AML or MDS-IB2	379	(30.1)	291	(89.8)	25	(3.4)
MM	374	(29.7)			370	(51.0)
Lymphoma	351	(27.9)			317	(43.7)

ALL	80	(6.4)	12	(3.7)	4	(0.6)
Other	75	(6.0)	21	(6.5)	10	(1.4)
Chemotherapy regimens						
AML - Induction						
Standard protocols[c]	411	(20.9)	411	(61.8)		
Purine-based chemotherapy[d]	254	(12.9)	254	(38.2)		
Auto-HCT						
BEAM conditioning[e]	289	(14.7)			289	(37.2)
Non-BEAM conditioning[f]	487	(24.8)			487	(62.8)
ALL - Induction	47	(2.4)				
Other[g]	475	(24.2)	93	(14.0)		
Previous allogeneic HCT	69	(3.5)	44	(6.6)	1	(0.1)
Days in hospital (median, IQR)	26	(16)	33	(16)	20	(7)
Days of neutropenia (median, IQR)	10	(13)	21	(14)	7	(3)
Neutropenic enterocolitis	178	(9.1)	92	(13.8)	74	(9.5)

ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; HCT: hematopoietic cell transplantation; IQR: interquartile range; MDS-IB2: myelodysplastic syndrome with increased blasts 2; MM: multiple myeloma.

[a] Continuous variables are described using medians and interquartile ranges and categorical variables using numbers and percentages (%).

[b] Demographic characteristics, chronic health conditions and underlying malignancies are reported by patient (not by chemotherapy course).

[c] All standard inductions regimens included standard-dose cytarabine with anthracyclines (mostly idarubicine or daunorubicine, "7+3") for the first induction cycle and high-dose cytarabine +/- amsacrine or daunorubicin for the second induction cycle, according to specific HOVON/SAKK protocols [20].

[d] Purine-based chemotherapy regimens included fludarabine, or seldomly cladribine, with high-dose cytarabine, and G-CSF +/- idarubicine for FLAG(-Ida), respectively CLAG(-Ida) protocols [21–25].

[e] BEAM regimen included carmustine, etoposide, cytarabine and melphalan [15].

[f] Other conditioning regimens included melphalan or other chemotherapies [15].

[g] Other chemotherapies included those administrated for multiple myeloma or non-Hodgkin's lymphoma / Hodgkin's lymphoma, or consolidation regimens for acute leukemia

Table 2. Risk factors for neutropenic enterocolitis in acute myeloid leukemia induction.

Characteristics[a]	**All AML induction courses (N=665)**									
	No NEC (N=573)		**NEC (N=92)**		**Univariate**			**Multivariate** [e]		
	N	**%**	**N**	**%**	**OR**	**(95%CI)**	**P**	**OR**	**(95%CI)**	**P**
Age, years (median, IQR)	57	(19.3)	54	(17.2)	0.99	(0.98-1.01)	0.5			
Gender, male	348	(60.7)	57	(62.0)	1.05	(0.67-1.66)	0.8			
Ethnicity, Caucasian	548	(95.6)	89	(96.7)	1.35	(0.40-4.58)	0.6			
Chronic health conditions										
Cardiac insufficiency	68	(11.9)	11	(12.0)	1.01	(0.51-1.99)	0.9			
Pulmonary disease	67	(11.7)	6	(6.5)	0.53	(0.22-1.25)	0.1			
Chronic renal failure	24	(4.2)	1	(1.1)	0.25	(0.03-1.88)	0.2			
Neurological disease	21	(3.7)	2	(2.2)	0.58	(0.13-2.53)	0.5			
Diabetes mellitus	35	(6.1)	4	(4.4)	0.70	(0.24-2.01)	0.5			
Tobacco use	172	(30.0)	30	(32.6)	1.13	(0.70-1.81)	0.6			
Prognostic score of AML[b]										
Favorable-risk	92	(20.2)	16	(20.3)	Ref.					

Intermediate-risk	179	(39.3)	27	(34.2)	0.87	(0.44-1.69)	0.7			
Poor-risk	185	(40.6)	36	(45.6)	1.12	(0.59-2.12)	0.7			
Blasts counts at admission										
<20 G/L	380	(66.3)	49	(53.3)	Ref.					
20-50 G/L	120	(20.9)	22	(23.9)	1.42	(0.83-2.45)	0.2			
>50 G/L	73	(12.7)	21	(22.8)	2.23	(1.26-3.94)	**0.006**	2.02	(1.15-3.56)	**0.02**
Chemotherapy regimen[c]										
Standard induction	336	(58.6)	75	(81.5)	Ref.					
Purine-based chemotherapy	237	(41.4)	17	(18.5)	0.32	(0.19-0.56)	**<0.001**	0.27	(0.15-0.47)	**<0.001**
Duration of agranulocytosis										
<10 days	35	(6.1)	4	(4.4)	Ref.					
11-25 days	336	(58.6)	57	(62.0)	1.48	(0.51-4.34)	0.5			
>25 days	202	(35.3)	31	(33.7)	1.34	(0.45-4.04)	0.6			
Other agents or conditions										
Azacitidine	22	(3.8)	8	(8.7)	2.39	(1.03-5.53)	**0.04**	2.45	(1.01-5.90)	**0.05**
Hydroxycarbamide	81	(14.1)	21	(22.8)	1.80	(1.05-3.08)	**0.03**			
Corticosteroids > 100mg[d]	260	(45.4)	56	(60.9)	1.87	(1.19-2.94)	**0.006**	2.07	(1.29-3.30)	**0.002**
Anti *Candida* prophylaxis	439	(76.6)	71	(77.2)	1.03	(0.61-1.74)	0.9			
G-CSF	459	(80.1)	74	(80.4)	1.02	(0.59-1.78)	0.9			
Previous NEC	55	(9.6)	11	(12.0)	1.28	(0.64-2.55)	0.5			

AML: acute myeloid leukemia; CI: confidence interval; G-CSF: granulocyte-colony stimulating factor; IQR: interquartile range; NEC: neutropenic enterocolitis; OR: odds ratio; Ref: reference.

[a] Continuous variables are described using medians and interquartile ranges, and categorical variables are described using numbers and proportions (%). Characteristics are reported by chemotherapy episode.

[b] Prognostic score classification according to the 2017 European Leukemia Network [29]. Data were missing in 130 patients.

[c] All standard induction regimens included standard-dose cytarabine with anthracyclines (mostly idarubicine or daunorubicine, "7+3") for the first induction cycle and high-dose cytarabine +/- amsacrine or daunorubicin for the second induction cycle, according specific HOVON/SAKK protocol [20]. Purine-based chemotherapy regimens included fludarabine, or seldomly cladribine, with high-dose cytarabine, and G-CSF +/- idarubicine for FLAG(-Ida), respectively CLAG(-Ida) protocols [21–25].

[d] Total dose of corticosteroid during chemotherapy episode were calculated in prednisone equivalents : hydrocortisone (x 0.3), prednisolone (x 1), methylprednisolone (x 1.25), dexamethasone or betamethasone (x 6.7) [30].

[e] Variables with a P value <0.1 were entered into multivariable models and subsequently selected by using the stepwise program implemented in Stata®, with backward removal of variable with a P value <0.1. Hydroxycarbamide was excluded from the analysis due to collinearity with blastosis.

Table 3. Risk factors for neutropenic enterocolitis in acute myeloid leukemia induction (subgroup of patients treated with "standard" induction protocols).

Characteristics[a]	**All induction courses (N=411)**									
	No NEC (N=336)		**NEC (N=75)**		**Univariate (N=411)**			**Multivariate (N=411)**		
	N0	**N0%**	**N1**	**N1%**	**OR**	**(95%CI)**	**P**	**OR**	**(95%CI)**	**P**
Age, years (median, IQR)	56	(19)	55	(18)	1.00	(0.98-1.02)	0.8			
Gender, male	196	(58.3)	47	(62.7)	1.20	(0.72-2.01)	0.5			
Ethnicity, Caucasian	321	(95.5)	73	(97.3)	1.71	(0.38-7.62)	0.5			

Chronic health conditions									
Cardiac insufficiency	34	(10.1)	10	(13.3)	1.37 (0.64-2.91)	0.4			
Pulmonary disease	36	(10.7)	5	(6.7)	0.60 (0.23-1.57)	0.3			
Chronic renal failure	13	(3.9)	1	(1.3)	0.34 (0.04-2.61)	0.3			
Neurological disease	12	(3.6)	1	(1.3)	0.36 (0.05-2.85)	0.3			
Diabetes mellitus	18	(5.4)	3	(4.0)	0.74 (0.21-2.57)	0.6			
Tobacco use	101	(30.1)	26	(34.7)	1.23 (0.73-2.10)	0.4			
Prognostic score of AML[b]									
Favorable-risk	59	(21.3)	14	(20.6)	Ref.				
Intermediate-risk	116	(41.9)	25	(36.8)	0.91 (0.44-1.88)	0.8			
Poor-risk	102	(36.8)	29	(42.7)	1.20 (0.59-2.45)	0.6			
Blasts at admission									
<20 G/L	245	(72.9)	39	(52.0)	Ref.				
20-50 G/L	51	(15.2)	21	(28.0)	2.59 (1.41-4.76)	**0.002**	2.64	(1.37-5.08)	**0.004**
>50 G/L	40	(11.9)	15	(20.0)	2.36 (1.19-4.66)	**0.014**	2.25	(1.08-4.69)	**0.03**
HOVON-based regimen[c]									
ARA-C alone	35	(10.4)	6	(8.0)	Ref.				
ARA-C with daunorubicin	98	(29.2)	15	(20.0)	0.89 (0.32-2.48)	0.8			
ARA-C with idarubicin	132	(39.3)	32	(42.7)	1.41 (0.55-3.65)	0.5	2.66	(1.31-5.41)	**0.007**
ARA-C with amsacrine	71	(21.1)	22	(29.3)	1.81 (0.67-4.86)	0.2	3.24	(1.54-6.84)	**0.002**
Second (versus first) induction	148	(44.1)	32	(42.7)	0.95 (0.57-1.57)	0.8			
Duration of agranulocytosis									
<10 days	15	(4.5)	2	(2.7)	Ref.				
11-25 days	177	(52.7)	48	(64.0)	2.03 (0.45-9.20)	0.4			
>25 days	144	(42.9)	25	(33.3)	1.30 (0.28-6.05)	0.7			
Other agents or conditions									
Azacitidine	10	(3.0)	6	(8.0)	2.83 (1.00-8.06)	0.05	3.29	(1.03-10.5)	**0.04**
Hydroxycarbamide	50	(14.9)	19	(25.3)	1.94 (1.06-3.54)	**0.03**			
Corticosteroids > 100mg[d]	129	(38.4)	44	(58.7)	2.28 (1.37-3.79)	**0.002**	2.77	(1.57-4.88)	**<0.001**
Anti *Candida* prophylaxis	264	(78.6)	57	(76.0)	0.86 (0.48-15.6)	0.6			
G-CSF	232	(69.1)	57	(76.0)	1.42 (0.80-2.53)	0.2			
Previous NEC	20	(6.0)	10	(13.3)	2.43 (1.09-5.44)	**0.03**	3.65	(1.48-9.04)	**0.005**

AML: acute myeloid leukemia; CI: confidence interval; G-CSF: granulocyte-colony stimulating factor; IQR: interquartile range; NEC: Neutropenic enterocolitis; OR: Odd Ratio; Ref: Reference.

[a] Continuous variables are described using medians and interquartile ranges, and categorical variables are described using numbers and proportions (%). Characteristics are reported by chemotherapy episode.

[b] Prognostic score classification according to the 2017 European Leukemia Network [29]. Data were missing in 66 patients.

[c] All standard inductions regimens included standard-dose cytarabine with anthracyclines (mostly idarubicine or daunorubicine, "7+3") for the first induction cycle and high-dose cytarabine +/- amsacrine or daunorubicin for the second induction cycle, according the number of the HOVON/SAKK protocol [20].

[d] Total dose of corticosteroid during chemotherapy episode were calculated in prednisone equivalents : hydrocortisone (x 0.3), prednisolone (x 1), methylprednisolone (x 1.25), dexamethasone or betamethasone (x 6.7) [30].

[e] Variables with a P value <0.25 were entered into multivariable models and subsequently selected by using the stepwise program implemented in Stata®, with backward removal of variable with a P value <0.1. Hydroxycarbamide was excluded from the analysis due to collinearity with blastosis.

Table 4. Risk factors for neutropenic enterocolitis in autologous HCT.

Characteristics[a]	All auto-HCT courses (N=776)									
	No NEC (N=702)		NEC (N=74)		Univariate (N=776)			Multivariate[†] (N=775)		
	N	(%)	N	(%)	OR	(95%CI)	P	OR	(95%CI)	P
Age, years (median, IQR)	57	(13.7)	60	(10.4)	1.02	(1.00-1.04)	0.1	1.03	(1.01-1.06)	**0.007**
Gender, male	425	(60.5)	48	(64.9)	1.20	(0.73-1.99)	0.5			
Ethnicity, Caucasian	634	(90.3)	66	(89.2)	0.88	(0.41-1.92)	0.8			
Chronic health conditions										
Cardiac insufficiency	65	(9.3)	10	(13.5)	1.53	(0.75-3.13)	0.2			
Pulmonary disease	58	(8.3)	7	(9.5)	1.16	(0.51-2.64)	0.7			
Chronic renal failure	39	(5.6)	6	(8.1)	1.50	(0.61-3.67)	0.4			
Neurological disease	36	(5.1)	3	(4.1)	0.78	(0.23-2.60)	0.7			
Diabetes mellitus	63	(9.0)	4	(5.4)	0.58	(0.20-1.64)	0.3			
Tobacco use	149	(21.2)	16	(21.6)	1.02	(0.57-1.83)	0.9			
Underlying disease										
Multiple myeloma	394	(56.1)	26	(35.1)	Ref.					
Lymphoma [b]	273	(38.9)	44	(59.5)	2.44	(1.47-4.06)	**0.001**			
Hodgkin lymphoma	225	(32.1)	35	(47.3)	2.36	(1.38-4.02)	0.002			
Non-Hodgkin lymphoma	48	(6.8)	9	(12.2)	2.84	(1.26-6.42)	0.012			
Other [c]	35	(5.0)	4	(5.4)	1.73	(0.57-5.24)	0.3			
Chemotherapy regimen[d]										
Non-BEAM	457	(65.1)	30	(40.5)	Ref.					
BEAM	245	(34.9)	44	(59.5)	2.74	(1.68-4.46)	**<0.001**	3.28	(1.98-5.43)	**<0.001**
Duration of agranulocytosis										
0-10 days	666	(94.9)	66	(89.2)	Ref.					
>10 days	36	(5.1)	8	(10.8)	2.24	(1.00-5.02)	0.05			
Other agents or conditions										
Corticosteroids > 250mg[e]	483	(68.8)	57	(77.0)	1.52	(0.86-2.67)	0.1			
G-CSF	694	(98.9)	73	(98.7)	0.84	(0.10-6.82)	0.9			
Previous NEC	2	(0.3)	0	(0)						

CI: confidence interval; HCT: hematopoietic cell transplantation; IQR: interquartile range; NEC: Neutropenic enterocolitis; OR: Odd Ratio; Ref: Reference.

[a] Continuous variables are described using medians and interquartile ranges, and categorical variables are described using numbers and proportions (%). Characteristics are reported by 776 chemotherapy episodes in 726 patients.

[b] Non-Hodgkin lymphoma (N=260) had a NEC incidence of 16% and Hodgkin lymphoma (N=57) had a NEC incidence of 13%

[c] Acute myeloid leukemia (N=26), acute lymphoblastic leukemia (N=6), chronic lymphoblastic leukemia (N=1), POEMS syndrome (N=2), myelodysplastic syndrome (N=1), multifocal plasmocytoma (N=1), amyloidosis (N=1), lymphomatous granulomatosis (N=1)

[d] BEAM regimen included BiCNU or carmustine, etoposide, cytarabine and melphalan and was administered almost exclusively to patients with lymphoma (N=285) [15]. Non-BEAM regimens included mostly melphalan (for multiple myeloma) (N=428) and other chemotherapies (N=59), including busulfan-melphalan (Bu-Mel, N=26), BiCNU-Thiothepa (N=26), cyclophosphamide-etoposide (N=4) and cyclophosphamide-total body irradiation (N=3).

[e] Total dose of corticosteroid during chemotherapy episode were calculated in prednisone equivalents : hydrocortisone (x 0.3), prednisolone (x 1), methylprednisolone (x 1.25), dexamethasone or betamethasone (x 6.7) [30].

[f] Variables with a P value <0.2 were entered into multivariable models and subsequently selected by using the stepwise program implemented in Stata®, with backward removal of variable with a P value <0.1.

Table 5. Comparative outcomes of patients with and without neutropenic enterocolitis according to chemotherapy regimens.

	AML induction					HCT				
	No NEC		NEC			No NEC		NEC		
Characteristics[a]	**N**	**%**	**N**	**%**	**P**	**N**	**%**	**N**	**%**	**P**
Chemotherapy episodes	573		92			702		74		
Days in hospital, median (IQR)	32	(17)	34	(25)	**0.03**	20	(6)	26	(8)	**<0.001**
Associated infections[b]										
Bacteremia	295	(51.5)	50	(54.3)	0.6	157	(22.4)	17	(23.0)	0.9
Gram-negative bacilli	128	(22.3)	20	(21.7)	0.9	85	(12.1)	8	(10.8)	0.7
Gram-positive cocci	147	(25.7)	35	(38.0)	**0.01**	56	(8)	7	(9.5)	0.7
Anaerobes	21	(3.7)	1	(1.1)	0.2	4	(0.6)	1	(1.4)	0.4
Polymicrobial	141	(24.6)	20	(21.7)	0.6	88	(12.5)	9	(12.2)	0.9
Fungemia	4	(0.7)	6	(6.5)	**<0.001**	4	(0.6)	3	(4.1)	**0.01**
Hepatosplenic candidiasis[c]	9	(1.6)	2	(2.2)	0.7					
Invasive mold infection[d]										
Pulmonary	40	(7.0)	11	(12.0)	0.1	1	(0.1)			
Digestive	1	(0.2)	1	(1.1)[e]	0.2					
Sepsis severity scores[f]										
Quick SOFA ≥ 2[g]	65	(11.3)	18	(19.6)	**0.03**	38	(5.4)	17	(23.0)	**<0.001**
SOFA[h]										
<5	511	(89.2)	84	(91.3)	Ref.	674	(96)	60	(81.1)	Ref.
5-10	56	(9.8)	4	(4.3)	0.1	25	(3.6)	11	(14.9)	**<0.001**
>10	6	(1.0)	4	(4.3)	**0.03**	3	(0.4)	3	(4.1)	**0.003**
Transfer to ICU[i]	42	(7.3)	13	(14.1)	**0.03**	14	(2.1)	14	(18.9)	**<0.001**
Abdominal surgery	5	(0.9)	3	(2.2)	0.07			1	(1.4)	
In hospital all-causes mortality[j]	14	(2.4)	6	(6.5)	**0.04**	3	(0.4)	1	(1.4)	0.3

ICU: intensive care unit; IQR: interquartile range; NEC: Neutropenic enterocolitis; ref: Reference; SOFA: sequential organ failure assessment.

[a] Continuous variables are described using medians and interquartile ranges, and categorical variables are described using numbers and proportions (%). Characteristics are reported by NEC episodes.

[b] Infections identified during the entire hospital stay.

[c] In the standard induction AML group, 1/8 and 1/2 had concomitant fungemia in the no NEC group and NEC group respectively. In the purine-based chemotherapy group, no concomitant fungemia was documented.

[d] Among invasive filamentous fungal infections, the number of invasive aspergillosis was 27/34 in standard AML induction and 16/25 in purine-based chemotherapy for AML.

[e] EN was complicated by suspected or confirmed abdominal mold infections in 1 patient who died.

[f] Worse severity score during neutropenic episode.

[g] The QuickSOFA score [28] ranged from 0 to 3 according to presence or absence of these criteria: systolic blood pressure ≤100mmHg, tachypnea ≥22 breath per min and Glasgow coma score ≤14 (one point each); patients who did not develop fever and/or symptoms suggestive of sepsis were allocated the minimal score.

[h] Patients who did not develop fever and/or symptoms suggestive of sepsis are in the lower score group (<5).

[ih] All-causes of ICU admission during the hospital course.

[j] All-causes of mortality; see Figure 2 for Kaplan-Maier survival estimates.