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ORIGINAL ARTICLE

Neutropenia occurrence and predictors of reduced chemotherapy delivery: results from the INC-EU prospective observational European neutropenia study

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Abstract
Goals of work Neutropenia is a life-threatening, dose-limiting toxicity of many chemotherapy regimens. The goals of this study were to assess the incidence and risk of chemotherapy-induced neutropenia, febrile neutropenia (FN) and dose limitations in breast cancer and lymphoma patients undergoing chemotherapy in Europe.
Patients and methods Four hundred forty-four breast cancer and 305 lymphoma patients undergoing chemotherapy at 66 practices in five European countries participated in this prospective, observational study. Predictors of impaired chemotherapy delivery were investigated using a logistic regression model.
Main results In breast cancer, FN incidence was low (6%); however, grade 4 neutropenia was frequent (34%). Lymphoma patients experienced higher incidences of FN (non-Hodgkin lymphoma (NHL) 22%; Hodgkin lymphoma (HL) 15%) and grade 4 neutropenia (NHL 54%; HL 40%). For both diseases, FN and grade 4 neutropenia were associated with low relative dose intensity (RDI). Multivariate regression models indicated that first cycle FN, age≥65 years and Eastern Co-operative Oncology Group>1 were associated with low RDI in breast

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cancer and lymphoma, while colony-stimulating factor (CSF) primary prophylaxis appeared to be protective in lymphoma only. Primary CSF prophylaxis was provided to 9% of breast cancer, 28% of NHL and 19% of HL patients.
Conclusions Neutropenia and low RDI remain serious problems in both breast cancer and lymphoma populations undergoing chemotherapy. Several risk factors which can trigger reduced chemotherapy delivery were identified. These results can support physicians in identifying patients most at risk of receiving impaired chemotherapy delivery who would benefit from suitable preventive measures.

Keywords Breast cancer · Lymphoma · Neutropenia · Risk model · Relative dose intensity

Introduction

Myelosuppression represents the major dose-limiting toxicity of anti-cancer chemotherapy [10]. Chemotherapy-induced neutropenia (CIN) can lead to febrile neutropenia (FN), which requires immediate hospitalisation and treatment with antibiotics for patients with increased risk of life-threatening infections [8, 10, 24]. The level of in-hospital mortality associated with patients who are hospitalised for FN is 9.5% on average and more than 21% for patients with co-morbidities [12].

Chemotherapy dose reductions and dose delays, as a result of CIN and FN, can lead to reduced patient survival [2–5, 13–15, 17]. The risk of CIN and FN is particularly high for elderly patients [1, 29, 33], which may account for a tendency to reduce chemotherapy treatment in this group [1, 15, 29].

Despite the potential consequences of myelosuppression, myelotoxic chemotherapy remains central to the current standard of care for breast cancer and lymphoma patients. Over the past decade, breast cancer chemotherapy regimens based on cyclophosphamide, methotrexate and fluorouracil (CMF) have been superseded by more efficacious, but still myelotoxic, anthracycline-based regimens, such as fluorouracil, epirubicin and cyclophosphamide (FEC) [1, 30, 34]. Increased myelotoxicity might occur due to the adoption of some taxane-based therapies, such as docetaxel, doxorubicin and cyclophosphamide (TAC) [1, 20], which was recently recommended in treatment guidelines for early node-positive breast cancer [23].

For patients with aggressive non-Hodgkin lymphoma (NHL), combination therapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) has been the standard treatment since its development in the 1970s [31]. The recent addition of rituximab to the regimen has further improved patient outcomes [6, 31], although both regimens carry a significant risk of neutropenia [1, 19, 33]. Dose-dense CHOP (CHOP-14; administered every 14 days, supported with colony-stimulating factor) has been shown to improve patient survival compared with the 21-day regimen in both young and old patients [26, 27]. The most commonly used chemotherapy regimens for patients with Hodgkin lymphoma (HL) are associated with a lower risk of neutropenia; doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) or Stanford V (mechlorethamine, doxorubicin, etoposide, vincristine, vinblastine, bleomycin and prednisone) are widely used for early-stage disease, whilst bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone (BEACOPP) is an additional option for advanced-stage disease [11, 21].

Primary prophylaxis with colony-stimulating factors (CSFs) reduces the risk of FN [1, 7, 22, 33] and related chemotherapy dose reductions [25]. Therefore, a major treatment goal is to identify patients most at risk of developing neutropenia and its consequences before they begin their chemotherapy treatment [18].

The Impact of Neutropenia in Chemotherapy—European (INC-EU) Study Group has pioneered this work within Europe, with the recent publication of a multi-national retrospective study addressing the incidence and risk factors of dose delays, dose reductions and hospitalisations related to neutropenia induced by adjuvant breast cancer chemotherapy [30]. Parallel retrospective studies in the US have resulted in similar advances for breast cancer and lymphoma patients [15, 17]. Although these studies are clearly informative, retrospective data are limited by centre-specific deficits and differences in data availability.

The present paper presents results from a prospective study; the INC-EU Prospective Observational European Neutropenia Study was conducted to assess the incidence and predictors of grade 3–4 neutropenia, FN and reduced chemotherapy administration for breast cancer and lymphoma patients undergoing chemotherapy in European community practices. This paper reports the incidences of CIN, FN and related hospitalisations in these patient groups, as well as patterns of CSF use and chemotherapy dose limitations. A logistic regression analysis of impaired chemotherapy delivery is also presented. Work on regression models of FN occurrence is ongoing.

Patients and methods

Study design and patient selection

This prospective study was conducted in 66 centres in Belgium, France, Germany, Spain and the UK. Ethical approval was obtained for all centres and all participants provided their informed consent. The design was observa-

tional, and treatment was as per normal institutional clinical practice with the exception of a complete blood count at the expected (protocol defined) absolute neutrophil count (ANC) nadir in cycle 1. Centres were required to record all blood counts taken during each patient's chemotherapy treatment.

Patients with a histologically confirmed diagnosis of malignancy were eligible for inclusion: Breast cancer patients requiring adjuvant or neo-adjuvant chemotherapy were accrued from the full range of stages I to III, fitting the primary tumour, nodes and metastasis classification of T 0–3, N 0–2, M 0. Stage 4 breast cancer patients were not included because these patients are often treated with less aggressive regimens with the intent of prolonging or improving quality of life, rather than cure. Lymphoma patients with HL stage I_B–IV or with NHL with an International Prognostic Index of 0–3 needing chemotherapy were also eligible. Adult participants (age 18 or older, without upper age limit) had to start a new myelosuppressive chemotherapy regimen sequence with at least four cycles planned. Prior or concurrent radiation therapy was allowed.

Key exclusion criteria were: active infection within 72 h prior to start of chemotherapy, conditions causing neutropenia, malignant conditions with myeloid characteristics, use of antibody-based or cell-based immunotherapies (with the exception of rituximab), history of stem cell or bone marrow transplantation and concurrent participation in phase I or phase II trials. Concomitant treatments deemed necessary to provide adequate supportive care were permitted. Patients were observed until the end of their chemotherapy regimen. Non-completion of planned chemotherapy regimens did not lead to exclusion from the study.

The primary endpoint was the incidence of grade 3 (ANC$<1.0\times10^9$/L) and grade 4 neutropenia (ANC$<0.5\times10^9$/L). Secondary endpoints included incidence of: FN (grade 4 neutropenia and temperature$\geq$38°C), chemotherapy cycle delays or dose reductions, relative dose intensity (RDI), neutropenia-related hospitalisations and patterns of CSF use.

Dose reductions were defined as a reduction of $\geq$10% of planned dose of at least one drug in at least one cycle; dose delays were defined as a delay of $\geq$4 days in at least one cycle. RDI was defined as the ratio of the drug dose

Table 1 Patient and disease characteristics of breast cancer and lymphoma patients

Characteristic		Breast cancer (*N*=444)	NHL (*N*=240)	HL (*N*=65)
Age, years; mean±SD (range)		53.5±10.2 (27–81)	63.2±12.9 (17–90)	39.2±17.5 (18–79)
Female gender, *n* (%)		444 (100)	105 (43.8)	28 (43.1)
Oestrogen receptor status positive, *n* (%)		297 (67.4[a])	–	–
HER2/Neu status, *n* (%)	0	199 (53.1[b])	–	–
	1+	54 (14.4[b])		
	2+	40 (10.7[b])		
	3+	82 (21.9[b])		
Disease stage at inclusion, *n* (%)	I	109 (24.9[c])	–	–
	II	241 (55.0[c])		
	III	88 (20.1[c])		
Ann Arbor staging, *n* (%)	I	–	42 (17.7[d])	6 (9.2)
	II		62 (26.2[d])	34 (52.3)
	III		39 (16.5[d])	12 (18.5)
	IV		94 (39.7[d])	13 (20.0)
B symptoms, *n* (%)		–	113 (47.7[d])	36 (55.4)
IPI index, *n* (%)	low (0–1)	–	75 (31.7[d])	–
	intermediate (2–3)		132 (55.7[d])	
	high (≥4)		30 (12.7[d])	
No. of co-morbidities (mean±SD, range)		1.6±2.1 0–11	2.1±2.1 0–11	0.9±1.3 0–6
Cardiovascular co-morbidity, *n* (%)		95 (21.4)	65 (27.1)	8 (12.3)
Renal co-morbidity, *n* (%)		13 (2.9)	16 (6.7)	1 (1.5)

NHL Non-Hodgkin lymphoma, *HL* Hodgkin lymphoma, *HER2* human epidermal growth factor receptor 2, *IPI* International Prognostic Index
[a] *n*=441 due to missing values
[b] *n*=375 due to missing values
[c] *n*=438 due to missing values
[d] *n*=237 due to missing values

actually administered in the actual time, over the planned dose in the planned time. Drug-specific RDIs obtained for each anti-malignant drug were averaged across each component of the chemotherapy regimen and across all planned chemotherapy cycles, regardless of whether they were administered or not. Corticosteroids and immunotherapeutic agents, including rituximab, were disregarded for RDI calculations. Low RDI was defined as RDI≤85%. Hospitalisations were classified as neutropenia-related or not. CSF use was defined as primary prophylaxis (CSF use in the first cycle before a documented grade 3–4 CIN occurred or denoted as primary prophylaxis by site) or other use (incorporating CSF prophylaxis in cycles other than the first and CSF use in treatment).

Statistical methods

Assuming a dropout rate of 10%, 450 breast cancer patients and 300 lymphoma patients were required to allow accurate estimation of the incidence of grade 3–4 CIN, with a 95% confidence interval (CI) width of ±6% for each patient group (assuming an incidence rate of 20–30% for breast cancer and 40–60% for lymphoma patients) and for detecting relationships between various covariates and the incidence of neutropenia with 90% statistical power (assuming an underlying odds ratio of 2.25). Data were summarised using descriptive statistics. Preparatory univariate testing and subsequent multivariate logistic regression, using generalised-estimation-equations-based robust standard errors to allow for clustering by study centre, were used to assess predictors of low RDI, separately for breast cancer and lymphoma patients.

Covariates assessed for their relationship with low RDI included demographic information, patient and disease characteristics, co-morbidities (number and type), baseline laboratory data (including blood counts and constituent biochemical data), planned and actual treatment characteristics and neutropenic events. Assumed direct correlates of RDI were not used as covariates.

All tests were two-sided at the 5% significance level. Two-sided 95% CIs are shown, except where otherwise stated. CI calculation for binary variables assumed a binomial distribution. Statistical analyses were performed using the STATA® version 9 statistical package.

Results

Patient characteristics

A total of 759 patients were enrolled between January 2004 and May 2005, of whom ten were not evaluable due to

Table 2 Treatment characteristics for breast cancer patients

Regimen group[a]	Number	Distribution %	Primary CSF prophylaxis %[c] (*n*)	Other CSF use[b] %[c] (*n*)
Total	444	100	9.3[d] (41)	24.4[d] (108)
Anthracycline based	312	70.3	4.5[d] (14)	23.2[d] (72)
AC	74	16.7	1.4[d] (1)	5.5[d] (4)
EC	38	8.6	10.5 (4)	31.6 (12)
FAC	11	2.5	0 (0)	0 (0)
FEC	152	34.2	6[d] (9)	31.1[d] (47)
E-CMF	34	7.7	0 (0)	23.5 (8)
Other	3	0.7	0 (0)	33.3 (1)
Anthracycline and taxane containing	112	25.2	22.3 (25)	31.3 (35)
Sequential starting with an anthracycline-based regimen and followed by a taxane	87	19.6	12.6 (11)	33.3 (29)
TAC	17	3.8	70.6 (12)	11.8 (2)
Other immediate anthracycline–taxane combinations	8	1.8	25.0 (2)	50.0 (4)
Taxane-based	2	0.5	0 (0)	0 (0)
CMF	18	4.1	11.1 (2)	5.6 (1)

CSF Colony-stimulating factor, *AC* adriamycin (doxorubicin) and cyclophosphamide, *EC* epirubicin and cyclophosphamide, *FAC* 5-fluorouracil, adriamycin (doxorubicin) and cyclophosphamide, *FEC* 5-fluorouracil, epirubicin and cyclophosphamide, *E-CMF* epirubicin, cyclophosphamide, methotrexate and 5-fluorouracil; *TAC* taxotere (docetaxel), adriamycin (doxorubicin) and cyclophosphamide; *CMF* cyclophosphamide, methotrexate and 5-fluorouracil

[a] Cycle length was 3 weeks for the majority of cases. AC: mostly doxorubicin 60 mg/m^2; cyclophosphamide 600 mg/m^2. EC: mostly epirubicin 90 mg/m^2; cyclophosphamide 600 mg/m^2. FEC: mostly 5-fluorouracil 500–600 mg/m^2; epirubicin 100 mg/m^2; cyclophosphamide 500–600 mg/m^2; cycle length of 4 weeks with drug administrations on cycle days 1 and 8 used in 11 cases. E-CMF: mostly epirubicin 100 mg/m^2 followed by classical four weekly CMF, oral or iv-based. Sequential regimens composed of an anthracycline-based regimen and a taxane: first part mostly AC, EC or FEC; second part mostly docetaxel 100 mg/m^2 or paclitaxel 175 mg/m^2. TAC: docetaxel 75 mg/m^2; doxorubicin 50 mg/m^2; cyclophosphamide 500 mg/m^2. CMF: classical four weekly CMF, oral or iv-based.

[b] Other colony-stimulating factor (CSF) use: secondary prophylaxis or treatment.

[c] Denominator values for calculations are the regimen n-values in column 2, except where indicated.

[d] Denominator *n*-value=442 (total) and 310 (anthracycline based); 73 (AC); 151 (FEC) due to missing values.

Table 3 Treatment characteristics for lymphoma patients

Regimen group	Number	*Distribution* (%)	Primary CSF prophylaxis %[c] (*n*)	Other CSF use [a] %[c] (*n*)	Rituximab administration %[c] (*n*)
NHL					
Total	240	100	27.5 (66)	28.8 (69)	81.7 (196)
CHOP-21-like[b]	178	74.2	12.4 (22)	34.3 (61)	86.5 (154)
CHOP-14-like	41	17.1	75.6 (31)	9.8 (4)	65.9 (27)
ACVBP like	9	3.8	55.6 (5)	33.3 (3)	77.8 (7)
NHL other	12	5.0	66.7 (8)	8.3 (1)	66.7 (8)
HL					
Total	65	100	18.5 (12)	36.9 (24)	–
ABVD like	47	72.3	8.5 (4)	44.7 (21)	–
Hodgkin other	18	27.7	44.4 (8)	16.7 (3)	–
Stanford V	5	7.7	20.0 (1)	0 (0)	–
BEACOPP-like	8	12.3	62.5 (5)	25.0 (2)	–
ChlVPP-like	5	7.7	40.0 (2)	20.0 (1)	–

CSF Colony-stimulating factor, *CHOP* cyclophosphamide, hydroxydaunomycin (doxorubicin), oncovin (vincristine) and prednisone, *ACVBP* adriamycin (doxorubicin), cyclophosphamide, vindesine, bleomycin and prednisone, *NHL* non-Hodgkin lymphoma, *HL* Hodgkin lymphoma, *ABVD* adriamycin (doxorubicin), bleomycin, vinblastine and dacarbazine, *BEACOPP* bleomycin, etoposide, adriamycin (doxorubicin), cyclophosphamide, oncovin (vincristine), procarbazine and prednisone, *ChlVPP* chlorambucil, vinblastine, procarbazine and prednisone

[a] Other CSF use, non-primary prophylaxis or treatment.

[b] Includes six patients with a cycle length of 28 days.

[c] Denominator values for percentage calculations are the regimen *n*-values in column 2.

Table 4 Occurrence of neutropenia and FN by regimen for breast cancer and lymphoma patients

Regimen	Number	Any grade 4 neutropenia %[a] (95% CI)	Any FN %[a] (95% CI)	First cycle grade 4 neutropenia %[a] (95% CI)	First cycle FN %[a] (95% CI)
Breast cancer					
Total	444	34.4 (30.0–39.0)[b]	5.9 (3.9–8.5)[b]	24.4 (20.5–28.7)[b]	3.9 (2.3–6.1)[b]
Anthracycline based	312	36.7 (31.3–42.3)[c]	6.4 (4.0–9.8)[c]	28.5 (23.5–33.9)[c]	4.2 (2.3–7.1)[c]
Anthracycline and taxane containing excluding TAC	95	31.6 (22.4–41.9)	5.3 (1.7–11.9)	17.2 (10.2–26.4)[d]	3.2 (0.7–9.0)
TAC	17	43.8 (19.8–70.1)[e]	5.9 (0.1–28.7)	18.8 (4.0–45.6)[e]	5.9 (0.1–28.7)
CMF	18	5.6 (0.1–27.3)	0.0 (0.0–18.5)[g]	0.0 (0.0–18.5)[f,g]	0.0 (0.0–19.5)[f,g]
NHL					
Total	240	53.8 (47.2–60.2)	22.1 (17.0–27.9)	34.6 (28.6–41.0)	8.9 (5.5–13.1)
CHOP-21 like	178	53.4 (45.8–60.9)	21.9 (16.1–28.7)	34.8 (27.9–42.3)	9.6 (5.7–14.9)
CHOP-14 like	41	48.8 (32.9–64.9)	17.1 (7.2–32.1)	24.4 (12.4–40.3)	2.4 (0.1–12.9)
ACVBP like	9	88.9 (51.8–99.7)	44.4 (13.7–78.8)	77.8 (40.0–97.2)	0.0 (0.0–33.6)[g]
NHL other	12	50.0 (21.1–78.9)	25.0 (5.5–57.2)	33.3 (9.9–65.1)	25.0 (5.5–57.2)[d]
HL					
Total	65	40.0 (28.0–52.9)	15.4 (7.6–26.5)	24.6 (14.8–36.9)	6.2 (1.7–15.0)
ABVD like	47	34.0 (20.9–49.3)	14.9 (6.2–28.3)	21.3 (10.7–35.7)	8.5 (2.4–20.4)
HL other	18	55.6 (30.8–78.5)	16.7 (3.6–41.4)	33.3 (13.3–59.0)	0.0 (0.0–18.5)[d]

FN Febrile neutropenia, *TAC* taxotere (docetaxel), adriamycin (doxorubicin) and cyclophosphamide, *CMF* cyclophosphamide, methotrexate and 5-fluorouracil, *NHL* non-Hodgkin lymphoma, *CHOP* cyclophosphamide, hydroxydaunomycin (doxorubicin), oncovin (vincristine) and prednisone, *ACVBP* adriamycin (doxorubicin), cyclophosphamide, vindesine, bleomycin and prednisone, *HL* Hodgkin lymphoma, *ABVD* adriamycin (doxorubicin), bleomycin, vinblastine and dacarbazine; *CIN* chemotherapy-induced neutropenia

[a] Denominator values are regimen *n*-values except where indicated.

[b] Denominator *n*-value=442 (any grade IV CIN); 441 (any FN, cycle 1 FN); 438 (cycle 1 grade IV CIN) due to missing values.

[c] Denominator *n*-value=311 (any grade IV CIN); 310 (any FN, cycle 1 FN); 309 (cycle 1 grade IV CIN) due to missing values.

[d] Denominator *n*-value=93 due to missing values.

[e] Denominator *n*-value=16 due to a missing value.

[f] Denominator *n*-value=17 due to a missing value.

[g] One-sided 97.5% CI.

almost complete lack of data. Eight of these ten patients were found to be ineligible. The distribution of the remaining 749 patients was: Belgium, 105 (14%); France, 94 (13%); Germany, 306 (41%); Spain, 38 (5%); and UK, 206 (28%). Patient split by diagnosis was; breast cancer 444 (59%); NHL 240 (32%); HL 65 (9%). Four NHL patients were classified as relapsed leukaemias. Patient and disease characteristics are summarised in Table 1.

Treatment characteristics

Over 70% of breast cancer patients received anthracycline-based regimens, with FEC being the most frequent regimen (34%), followed by anthracycline–taxane regimens (25%; Table 2). Non-anthracycline, taxane-based and CMF regimens were used infrequently. The planned number of chemotherapy cycles (mean±SD) was 5.5±1.1 in those receiving non-sequential regimens and 7.9±0.8 in those receiving sequential regimens. Cycle length was usually 3 weeks. Primary prophylaxis with CSFs was generally low at 9%, although more than 70% of patients receiving TAC also received primary CSF prophylaxis (Table 2).

CHOP-21 and CHOP-14 regimens were used in 74% and 17% of NHL patients, respectively (Table 3). Rituximab use was high, averaging 82% across all NHL regimens. The planned number of chemotherapy cycles (mean±SD) was 6.2±1.5 and cycle length was usually 3 weeks. Twelve per cent of patients receiving CHOP-21 regimens and 76% of patients on the dose-dense CHOP-14 regimens received prophylactic CSF support from the first cycle (Table 3).

The majority of HL patients received ABVD-like regimens (72%), with BEACOPP being the second most common category (12%; Table 3). The planned number of chemotherapy cycles (mean±SD) was 5.4±1.7 and cycle length was usually 4 weeks. Primary prophylactic CSF use for HL patients averaged at 19%, ranging from 9% for ABVD-like regimens to 63% for BEACOPP-like regimens.

Incidence of neutropenia and FN

Table 4 details the incidence of neutropenia and FN across all cycles of chemotherapy and during the first cycle. Grade 3–4 neutropenia occurred in 64% of breast cancer patients, with 34% experiencing grade 4 CIN; in contrast, FN occurred in only 6% of breast cancer patients. The incidence of grade 3–4 neutropenia was 72% for NHL patients (54% experienced grade 4) and 75% for HL

Table 5 Occurrence of chemotherapy dose limitations in breast cancer and lymphoma patients

Regimen group	N	Dose delay ≥ 4 days[a] %[d] (95% CI)	Dose reduction ≥ 10%[b] %[d] (95% CI)	RDI ≤ 85%[c] %[d] (95% CI)
Breast cancer				
Total	444	35.1 (30.7–39.8)	14.2 (11.1–17.8)	21.4 (17.7–25.5)
Anthracycline based	312	36.5 (31.2–42.1)	12.2 (8.8–16.3)	22.4 (17.9–27.5)
Anthracycline- and taxane containing excluding TAC	95	32.6 (23.4–43.0)	20.0 (12.5–29.5)	16.8 (9.9–25.9)
TAC	17	29.4 (10.3–56.0)	17.6 (3.8–43.4)	29.4 (10.3–56.0)
CMF	18	22.2 (6.4–47.6)	11.1 (1.4–34.7)	11.1 (1.4–34.7)
NHL				
Total	240	45.8 (39.4–52.4)	33.3 (27.4–39.7)	36.3 (30.2–42.7)
CHOP-like three weekly	178	46.1 (38.6–53.7)	35.4 (28.4–42.9)	33.2 (26.3–40.6)
CHOP-like two weekly	41	46.3 (30.7–62.6)	24.4 (12.4–40.3)	43.9 (28.5–60.3)
ACVBP like	9	44.4 (13.7–78.8)	44.4 (13.7–78.8)	55.6 (21.2–86.3)
NHL other	12	41.7 (15.2–72.3)	25.0 (5.5–57.2)	41.7 (15.2–72.3)
HL				
Total	65	60.0 (47.1–72.0)	46.2 (33.7–59.0)	32.3 (21.2–45.1)
ABVD like	47	66.0 (50.7–79.1)	36.2 (22.7–51.5)	29.8 (17.3–44.9)
Other	18	44.4 (21.5–69.2)	72.2 (46.5–90.3)	38.9 (17.3–64.3)

CI Confidence interval, *RDI* relative dose intensity; *TAC* taxotere (docetaxel), adriamycin (doxorubicin) and cyclophosphamide; *CMF* cyclophosphamide, methotrexate and 5-fluorouracil, *NHL* non-Hodgkin lymphoma, *CHOP* cyclophosphamide, hydroxydaunomycin (doxorubicin), oncovin (vincristine) and prednisone; *ACVBP* adriamycin (doxorubicin), cyclophosphamide, vindesine, bleomycin and prednisone; *HL* Hodgkin lymphoma; *ABVD* adriamycin (doxorubicin), bleomycin, vinblastine and dacarbazine

[a] In at least one cycle.

[b] In at least one anti-malignant drug and at least one cycle.

[c] RDI was corrected for planned but non-administered cycles.

[d] Denominator values are regimen *n*-values.

patients (40% experienced grade 4). FN occurred in 22% of patients with NHL and 15% of HL patients. For both breast cancer and lymphoma patients, a high proportion of neutropenic events occurred during the first cycle of chemotherapy. Neutropenia-related hospitalisations occurred in 18% of NHL patients, 14% of HL patients and 5% of breast cancer patients.

Chemotherapy dose limitations

Eighty-six per cent of breast cancer patients received their planned number of chemotherapy cycles. More than one in five patients experienced some form of dose limitation. Dose delays≥4 days occurred in 35% of patients, dose reductions of ≥10% occurred in 14% of patients and 21% of the breast cancer patients received RDI≤85% (Table 5). For lymphoma, 72% of NHL patients completed their planned treatment cycles; dose delays occurred in 46% of patients, dose reductions in 33% of patients and 36% of NHL patients received RDI≤85%. In HL patients, 85% of whom completed their planned treatment cycles, dose delays occurred in 60% of patients, dose reductions in 46% and RDI≤85% occurred in 32% of patients (Table 5).

Predictors of impaired chemotherapy delivery

The occurrence of CIN and FN had an impact on chemotherapy delivery. Figure 1 shows the results of a univariate analysis of the effects of grade 4 neutropenia and FN on the proportion of breast cancer and NHL patients experiencing dose delays, dose reductions and low RDI. Both groups were more likely to experience a dose delay if they also experienced grade 4 neutropenia, compared to patients with no neutropenic events ($p<0.05$ and $p<0.01$, respectively). For breast cancer patients, dose reductions

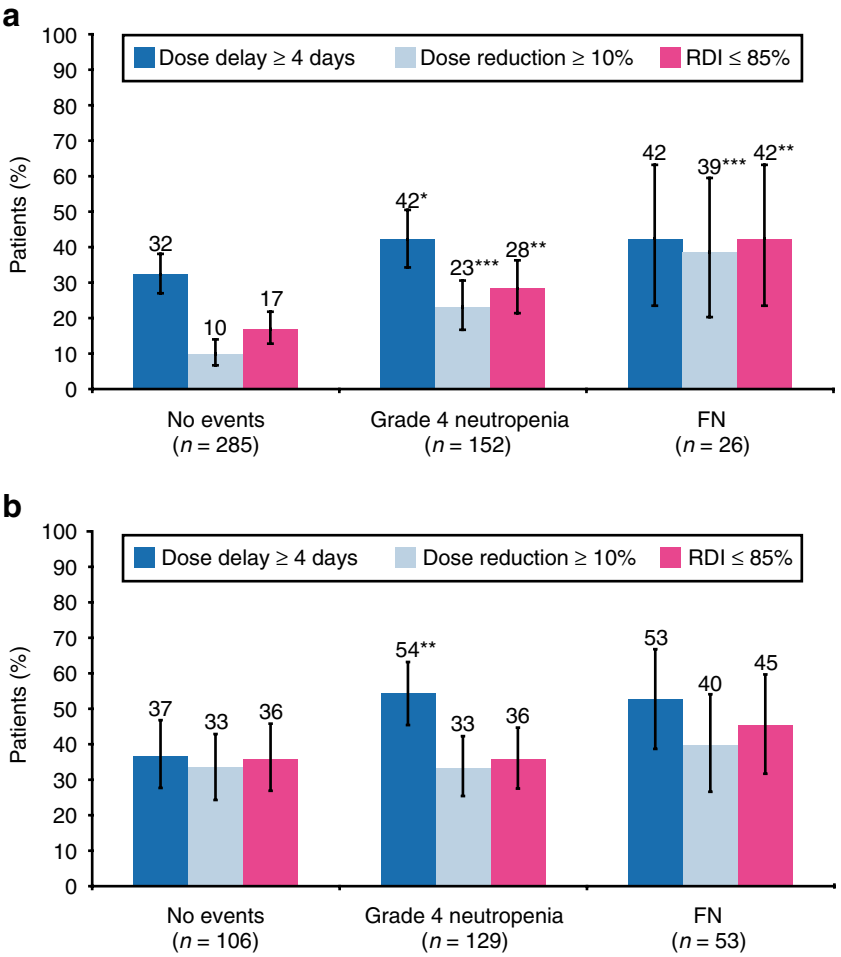

Fig. 1 Chemotherapy dose delays and reductions by neutropenic event. Data are shown for breast cancer patients (**a**) and NHL patients (**b**). Data represent univariate analyses and are not adjusted for confounding factors. Error bars represent 95% CIs. * $p<0.05$, ** $p<0.01$, *** $p<0.001$, when compared to patients with no events

and low RDI were more common in patients who experienced either grade 4 neutropenia or FN ($p<0.001$ and $p<0.01$, for dose reductions and RDI≤85%, respectively). Overall, 28% of breast cancer patients and 36% of NHL patients who experienced grade 4 neutropenia received RDI≤85%. For breast cancer and NHL patients who experienced FN, RDI≤85% occurred in 42% and 45%, respectively.

Multivariate logistic regression analysis identified three covariates that were significantly associated with low RDI occurrence in the breast cancer as well as lymphoma populations and showed similar effect sizes: ECOG status> 1, age≥65 years and cycle 1 FN occurrence (Table 6). When grade 4 neutropenia occurrence in cycle 1 was used as an alternative predictor to the cycle 1 FN covariate, the resulting odds ratios were 1.94 (CI 1.22–3.07; $p=0.005$) in breast cancer and 1.37 (CI 0.80–2.35; $p=0.258$) in lymphoma. Primary CSF prophylaxis had a strong protective effect for lymphoma. No such association was observed for breast cancer; however, it is important to consider this result in the context of the FN risk for each disease entity and factors driving provision of CSF (Table 4; see "Discussion"). Type of chemotherapy regimen was also significantly associated with low RDI occurrence in lymphoma.

Discussion

This study assessed the incidences of CIN and FN and their consequences for chemotherapy delivery in breast cancer and lymphoma patients undergoing chemotherapy in European academic and community practices between 2004 and 2006.

A significant proportion of FN and grade 4 neutropenia occurred in the first cycle of chemotherapy for the majority of regimens considered. This finding is consistent with reports from other studies [9, 16, 28].

The incidence of FN for the most frequently used breast cancer regimens in European practice was low (6%). However, grade 4 neutropenia occurred in a high proportion of patients (34%) and significantly impacted upon chemotherapy delivery. Over 20% of breast cancer patients received RDI≤85%, which has been shown to impact on survival [5].

Over 20% of NHL patients and 15% of HL patients developed FN at some point during the course of their chemotherapy treatment. Many lymphoma patients (54% of NHL and 40% of HL patients) also experienced grade 4 neutropenia, which was associated with delays in planned chemotherapy treatment. Dose reductions were also frequent in this patient group; overall, 30% of lymphoma patients received RDI≤85%. Recent results show that even reducing RDI to less than 90% can impact on survival in NHL patients receiving CHOP-21 [3].

A certain underestimation of neutropenia rates and, to a lesser extent, FN rates may have occurred because the frequency of blood counts was according to local institutional practice (apart from the protocol-specified blood count taken at cycle 1 nadir). However, the observed FN rates were generally in the range expected by current European Organisation for Research and Treatment of Cancer and American Society of Clinical Oncology guidelines [1, 33]. The FN risk of patients treated with anthracycline-based regimens was <10%. Regimens with concomitant anthracyclines and taxanes that have a high (> 20%) generic FN risk, such as TAC, were appropriately supported by primary CSF prophylaxis in most cases. CHOP-21-like regimens were expected to have an intermediate to high risk of FN (17–50%) [1]. In the present study, the overall FN rate for patients receiving CHOP-21-like regimens was 22% and primary CSF prophylaxis was provided to only 12% of these patients. This examination of the level of prophylactic CSF support provided to lymphoma patients, who frequently experienced CIN and FN, indicates that a shift in practice would be required if current European guidelines are to be followed [1].

Table 6 Multivariate models of low RDI occurrence

RDI≤85%	Breast cancer[a] OR (95% CI), *p*-value	Lymphoma[b] OR (95% CI), *p*-value
Age≥65 years	1.73 (1.12–2.70), 0.014	1.74 (1.12–2.70), 0.013
ECOG>1	4.13 (1.39–12.22), 0.010	2.42 (1.25–4.70), 0.009
Cycle 1 FN	3.68 (1.55–8.73), 0.003	2.27 (0.94–5.51), 0.069
Primary CSF prophylaxis	Ns	0.46 (0.23–0.93), 0.029
Regimen	Ns	
CHOP-14-like[c]		2.12 (0.85–5.27), 0.106
ACVBP like[c]		5.51 (2.27–13.39), <0.001
NHL other[c]		2.17 (0.58–8.06), 0.247
ABVD like[c]		1.12 (0.59–2.13), 0.719
Hodgkin other[c]		2.15 (0.86–5.33), 0.100

RDI Relative dose intensity, *OR* odds ratio, *CI* confidence interval, *ECOG* Eastern Co-operative Oncology Group, *FN* febrile neutropenia, *CSF* colony-stimulating factor, *ns* non-significant, *CHOP* cyclophosphamide, hydroxydaunomycin (doxorubicin), oncovin (vincristine) and prednisone; *ACVBP* adriamycin (doxorubicin), cyclophosphamide, vindesine, bleomycin and prednisone; *NHL* non-Hodgkin lymphoma; *ABVD* adriamycin (doxorubicin), bleomycin, vinblastine and dacarbazine

[a] $N=437$ due to missing values. Pseudo $R^2=0.027$. Robust standard error estimates adjusted for 39 clusters (centres).

[b] $N=304$ due to missing values. Pseudo $R^2=0.056$. Robust standard error estimates adjusted for 39 clusters (centres).

[c] Reference: CHOP-21-like chemotherapy. $p=0.008$ (Wald test based) for this set of parametres.

The practice of responding to FN by delaying or reducing chemotherapy has potentially serious consequences for patients including reduced survival [2, 3, 5]. Therefore, clinicians need to be made aware of the factors that can trigger chemotherapy dose limitations. We have modelled the factors associated with low RDI and shown that age≥65 years, ECOG>1 and cycle 1 FN are specific risk factors for low RDI in breast cancer as well as lymphoma populations. Our results are consistent with other risk models, as recently reviewed by Lyman et al. [18]. Age≥65 years has been identified as a risk factor for low RDI in both breast cancer [15, 19, 32] and NHL patients [17, 19]. Poor performance status has been identified as a risk factor for low RDI in patients with NHL [17] and the present results extend this finding to patients with breast cancer. We also specifically identified cycle 1 FN and cycle 1 grade 4 neutropenia as risk factors for low RDI, complementing the results of other studies [32]. The effect of these latter factors was stronger in the breast cancer population than in lymphoma where neutropenic events are more frequent and may be managed with greater routine. Further external validation of these findings is of importance.

Interestingly, in the regression models, a protective effect of primary CSF prophylaxis against low RDI was observed for lymphoma but not for breast cancer patients. This finding was unexpected and the most likely explanation is that most breast cancer patients received chemotherapy regimens with low FN risk, and primary CSF prophylaxis was only provided to those few patients who received high-risk regimens or was targeted to patients who did not require it. This selective use of CSF prophylaxis could not be represented in the model.

Choice of chemotherapy regimen is a key driver of adverse events including neutropenia and FN and therefore contributes to every patient's risk of low RDI. In this analysis, regimen type was a significant covariate in the lymphoma model but not in the breast cancer model. It appears that the breast cancer regimen types considered in this study had a similar potential to trigger low RDI, after modification by other factors (such as whether CSF prophylaxis was provided or not). In lymphoma, the set of covariates representing regimen types was statistically significant in its entirety and needed to be included in the model to avoid residual confounding. However, the individual coefficients were mostly non-significant and should be interpreted with great care.

The overall predictive ability of the low RDI models remained low, which is partially explained by a special characteristic. The factors identified here and in other published models of low RDI occurrence do not cause low RDI directly, they only influence clinical decision making, which is subject to substantial variation. Ultimately, low RDI is always a direct consequence of clinical decisions to dose delay or dose reduce (which are based on personal judgment and/or local institutional practice). Therefore, it would be difficult, and perhaps problematic, to construct clinical prediction rules for low RDI (while constructing prediction rules for other endpoints such as FN makes perfect sense). The contribution of low RDI models is to make clinicians aware of factors that often trigger decisions towards impaired chemotherapy delivery and thus, perhaps, to change clinical behaviours and improve patient management at both individual and institutional levels.

In sum, this prospective observational study provides information about the occurrence of CIN and FN in current European community practice and examines how neutropenic events and other factors impact upon chemotherapy delivery. The results indicate that neutropenia and impaired chemotherapy delivery remain serious problems in both breast cancer and lymphoma patient populations. Rather than acting to prevent, current clinical practice frequently delays or reduces chemotherapy, which may have severe long-term implications [2, 3, 5].

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