

SHORT REPORT

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Hodgkin lymphoma treatment with ABVD in the US and the EU: neutropenia occurrence and impaired chemotherapy delivery

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Abstract

Background: In newly diagnosed patients with Hodgkin lymphoma (HL) the effect of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD)-related neutropenia on chemotherapy delivery is poorly documented. The aim of this analysis was to assess the impact of chemotherapy-induced neutropenia (CIN) on ABVD chemotherapy delivery in HL patients.

Study design: Data from two similarly designed, prospective, observational studies conducted in the US and the EU were analysed. One hundred and fifteen HL patients who started a new course of ABVD during 2002-2005 were included. The primary objective was to document the effect of neutropenic complications on delivery of ABVD chemotherapy in HL patients. Secondary objectives were to investigate the incidence of CIN and febrile neutropenia (FN) and to compare US and EU practice with ABVD therapy in HL. Pooled data were analysed to explore univariate associations with neutropenic events.

Results: Chemotherapy delivery was suboptimal (with a relative dose intensity $\leq 85\%$) in 18-22% of patients. The incidence of grade 4 CIN in cycles 1-4 was lower in US patients (US 24% vs. EU 32%). Patients in both the US and the EU experienced similar rates of FN across cycles 1-4 (US 12% vs. EU 11%). Use of primary colony-stimulating factor (CSF) prophylaxis and of any CSF was more common in the US than the EU (37% vs. 4% and 78% vs. 38%, respectively). The relative risk (RR) of dose delays was 1.54 (95% confidence interval [CI] 1.08-2.23, $p = 0.036$) for patients with vs. without grade 4 CIN and the RR of grade 4 CIN was 0.35 (95% CI 0.12-1.06, $p = 0.046$) for patients with vs. without primary CSF prophylaxis.

Conclusions: In this population of HL patients, CIN was frequent and FN occurrence clinically relevant. Chemotherapy delivery was suboptimal. CSF prophylaxis appeared to reduce CIN rates.

Introduction

Combination therapy with doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) is the standard chemotherapy regimen for patients with Hodgkin lymphoma (HL) [1-3]. Myelosuppression, in particular neutropenia, is common during ABVD treatment [2]. Chemotherapy-induced neutropenia (CIN) can lead to febrile neutropenia (FN), which is associated with considerable morbidity, mortality and costs [4]. Standard care for the majority of FN patients requires hospitalisation and administration of intravenous antibiotics [5,6].

Neutropenic events often result in dose delays and dose reductions, leading to impaired chemotherapy delivery which has been associated with decreased survival in certain types of cancer [7-10], indicating that optimal intensity of chemotherapy treatment can improve patient outcomes [8]. Colony-stimulating factors (CSFs) have been shown to reduce the incidence and severity of neutropenic events across a broad range of malignancies and regimens and also to support the delivery of full chemotherapy dose intensity [5,11].

In patients with HL, the effect of ABVD-related neutropenia and neutropenic complications on chemotherapy delivery are poorly documented [2,12]. Two similarly designed, prospective, observational studies were conducted in the US [13] and Europe [14] to

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assess the incidence of neutropenia in patients undergoing chemotherapy. Here we present a subgroup analysis of HL patients from these studies. The primary objective was to assess the effects of neutropenic complications on the delivery of ABVD chemotherapy. Secondary objectives were to investigate the incidence of CIN and FN in patients with HL undergoing ABVD chemotherapy and to compare US and EU practice with ABVD therapy in HL.

Methods

Two similarly designed, prospective, observational studies [13,14] enrolled patients with solid tumours or lymphoma initiating a new course of chemotherapy, with at least 4 cycles planned, during the period 2002-2005. In the US, a total of 4458 patients were recruited from 115 community practices. In the EU, a total of 749 patients were recruited from 66 clinical centres in Belgium, France, Germany, Spain and the UK.

Patients eligible for inclusion in this subgroup analysis were adults aged ≥ 18 years about to start a new course of ABVD (patients in whom doxorubicin was replaced with epirubicin were also allowed). In the US study, patients had a minimum life expectancy of at least 3 months. In the EU study, patients had to be HL stage IB-IV. Prior chemotherapy and concurrent radiation therapy were permitted. Key exclusion criteria were: use of antibody-based or cell-based immunotherapies, a history of stem-cell or bone-marrow transplantation and HIV infection. Additionally, the US study excluded patients diagnosed with myeloma or treated for active infection and did not allow participation in double-blind clinical trials. Patients in the EU were excluded if they had conditions causing neutropenia, malignant conditions with myeloid characteristics, or active infection within 72 hours prior to the start of chemotherapy. Concurrent participation in phase I/II clinical trials was not permitted. Ethical approval was obtained for all centres and all participants provided informed consent.

Data were merged and variable definitions reconciled to form a single, pooled dataset. Body surface area was calculated using the Mosteller formula [15]. Delivery of chemotherapy was assessed by considering the proportion of patients that received relative dose intensity (RDI) $\leq 85\%$ of the planned or standard dose intensity and by documenting the occurrence of dose reductions $> 10\%$ and dose delays > 3 days. As delivery of vinblastine is unlikely to be affected by neutropenia, this agent was excluded from the calculation of RDI and dose reductions. In the US study, blood counts were drawn at the beginning of each cycle and at mid-cycle, for up to 4 cycles of treatment. In the EU study, a blood count at the expected (protocol defined) absolute neutrophil count (ANC) nadir was required in cycle 1. Centres

were also required to record all blood counts taken during each patient's chemotherapy treatment. Grades 3 and 4 CIN were defined as an ANC $< 1000/\text{mm}^3$ and $< 500/\text{mm}^3$ [16], respectively, and FN as ANC $< 1000/\text{mm}^3$ in combination with site-reported fever above 38°C and/or infection. Primary CSF prophylaxis was defined as CSF use in the first cycle of chemotherapy before a documented grade 3-4 CIN occurred or denoted as primary prophylaxis by the site.

Due to the limited sample size, analyses were predominantly descriptive. Univariate associations between variables were explored in the pooled dataset. Associations of binary data were expressed as relative risks with accompanying 95% confidence intervals. Significance testing was based on Fisher's exact test (2-sided) due to small sample size, which explains some apparent inconsistencies between p values and confidence limits.

Results

Patient characteristics

A total of 115 HL patients (68 US patients, 47 EU patients) met the eligibility criteria and were included in the analysis. The age range was 19-83 years (median 36) in US patients and 18-74 years (median 34) in EU patients; 49% of US patients and 38% of EU patients were female. US patients had slightly higher body surface area and higher incidence of stage III/IV disease than EU patients and were more often pre-treated with radiotherapy (Table 1). Eastern Cooperative Oncology Group performance status was similar between US and EU patients and no patients had prior chemotherapy.

Treatment characteristics

In most patients, 4-5 or 6 cycles of ABVD were planned. In the US and the EU, median planned dose intensities (expressed on the basis of actual body weight) met the ABVD standard of bleomycin, 5 units/ m^2/week ; doxorubicin, 12.5 mg/ m^2/week ; dacarbazine, 187.5 mg/ m^2/week ; and vinblastine, 3 mg/ m^2/week . Actual planned dose intensities deviated in a number of patients and resulting means were marginally higher in the EU patients (Table 1). One US patient (1.5%) and three EU patients (6.4%) received epirubicin instead of doxorubicin (EBVD).

The percentage of patients receiving CSF overall and as primary prophylaxis was higher for US patients (any CSF use: US 78% vs. EU 38%; primary CSF prophylaxis: US 37% vs. EU 4%). Antibiotic use was similar between the two populations (any antibiotic use: US 41% vs. EU 49%; primary prophylaxis with antibiotics: US 13% vs. EU 17%).

Chemotherapy delivery

Dose delays > 3 days were more frequently observed in EU patients and dose reductions $> 10\%$ were more frequent in US patients (Figure 1). Chemotherapy delivery

Table 1 Patient, disease and treatment characteristics

Characteristic		US (N = 68)	EU (N = 47)
Age in years, mean ± SD (range)		40.9 ± 16.2 (19-83)	37.9 ± 16.5 (18-74)
Female gender, N (%)		33 (48.5)	18 (38.3)
Race, N (%)	Caucasian/white	54 (79.4)	46 (97.9)
	Black	10 (14.7)	0 (0.0)
	Other	4 (5.9)	1 (2.1)
BSA at baseline in m ² , mean ± SD (range)		1.94 ± 0.26 (1.42-2.53)	1.85 ± 0.21 (1.41-2.28)
ECOG status, N (%)	0	47 (69.1)	30 (63.8)
	1	20 (29.4)	14 (29.8)
	2	1 (1.5)	3 (6.4)
Disease stage ¹ , N (%)	I	8 (12.1) ²	5 (10.6)
	II	30 (45.5) ²	28 (59.6)
	III	23 (34.8) ²	8 (17.0)
	IV	5 (7.6) ²	6 (12.8)
Prior radiotherapy, N (%)		6 (8.8)	0 (0.0)
Baseline WBC in 10 ³ /mm ³ , mean ± SD; median		9.4 ± 4.9; 7.8	9.5 ± 3.8; 8.4
Baseline ANC in 10 ³ /mm ³ , mean ± SD; median		6.5 ± 3.3; 5.3 ²	7.2 ± 3.6; 6.6
Diabetes, N (%)		8 (11.8)	0 (0.0)
Cardiac comorbidity, N (%)		0 (0.0)	2 (4.3)
Planned dose intensity in mg/m ² /week, mean ± SD; median	Bleomycin	4.9 ± 0.9; 4.9	5.3 ± 1.2; 5.0
	Doxorubicin	12.5 ± 1.9; 12.3	12.8 ± 2.7; 12.4 ³
	Dacarbazine	184.0 ± 29.5; 183.6	198.3 ± 50.2; 186.7
	Vinblastine	3.0 ± 0.5; 2.9	3.2 ± 0.8; 3.0
Planned cycle number, N (%)	≤ 3	0 (0.0)	2 (4.3)
	4-5	29 (42.6)	16 (34.0)
	6	38 (55.9)	26 (55.3)
	≥ 8	1 (1.5)	3 (6.4)
Planned cycle length in days, N (%)	14	7 (10.3)	5 (10.6)
	21	5 (7.4)	2 (4.3)
	28	56 (82.4)	40 (85.1)

BSA body surface area; ECOG Eastern Cooperative Oncology Group; WBC white blood cell count; ANC absolute neutrophil count.

¹ US: based on American Joint Committee Cancer staging; EU: based on Ann Arbor staging.

² N = 66 due to missing values.

³ N = 44 as 3 EU patients received epirubicin.

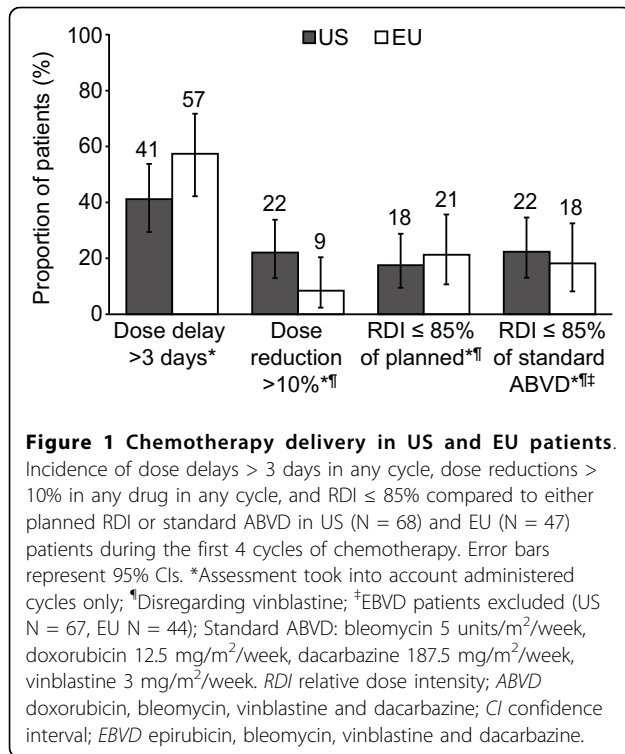
was suboptimal in 18-22% of patients (RDI ≤ 85% of ABVD standard). Comparison against the actual planned dose intensity for each individual patient led to a very similar result.

Incidence of neutropenia and FN

Patients in both the US and the EU experienced similar rates of FN in the first cycle of chemotherapy (US 7% vs. EU 9% EU) and across cycles 1-4 (US 12% vs. EU 11%). The incidence of CIN in cycles 1-4 was lower in US patients (Figure 2). US patients had a mean ANC nadir of 2000 ± 2300/mm³ in the first cycle compared to EU patients whose mean ANC nadir was 1300 ± 1000/mm³ in the first cycle.

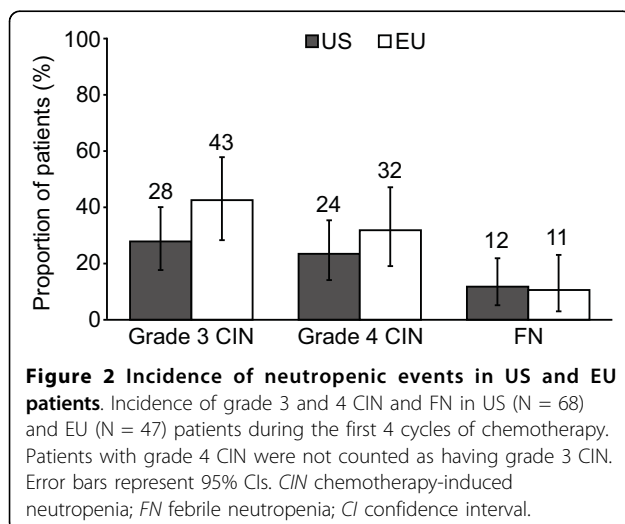
Factors associated with chemotherapy delivery in the pooled dataset

The relative risk (RR) of dose delays > 3 days was 1.54 (95% confidence interval [CI] 1.08-2.23, *p* = 0.036) for patients with vs. without grade 4 CIN. There was no evidence of an association between the presence of grade 4 CIN in any cycle and dose reductions > 10% or RDI ≤ 85% of planned/standard. Similarly, there was no evidence of an association between grade 4 CIN in cycle 1 and dose delays, dose reductions or RDI ≤ 85% of planned/standard. CSF primary prophylaxis was not associated with dose delays > 3 days, dose reduction > 10% or RDI ≤ 85% of planned/standard.



Association of CSF prophylaxis and neutropenic events in the pooled dataset

Patients receiving CSF primary prophylaxis were less likely to develop CIN than patients who did not receive CSF primary prophylaxis. The RR of grade 4 CIN in any cycle was 0.35 (95% CI 0.12-1.06, $p = 0.046$) for patients with vs. without primary CSF prophylaxis, and the RR of grade 3 or 4 CIN in any cycle was 0.42 (95% CI 0.23-0.76, $p < 0.001$). There was also a reduced risk of grade 3 or 4 CIN in cycle 1 for patients with vs. without CSF prophylaxis (RR 0.40, 95% CI 0.19-0.83, $p = 0.004$).



There was no evidence of an association between CSF primary prophylaxis and incidence of FN in cycle 1 or cycles 1-4. In cycle 1, FN incidence was 7% in 27 patients with CSF primary prophylaxis and 8% in 88 patients with no CSF primary prophylaxis (RR 0.93, 95% CI 0.21-4.22, $p = 1.000$). In cycles 1-4, corresponding incidences were 15% and 10% (RR 1.45, 95% CI 0.48-4.33, $p = 0.500$). The other univariate associations considered were not statistically significant.

Discussion

This study assessed the impact of CIN on ABVD chemotherapy delivery in HL patients in the EU and the US. Baseline characteristics were similar in both groups although US patients had a more advanced disease state. In both EU and US patients, CIN occurrence was substantial and the observed FN incidence of 11-12% was considerably higher than the 4% reported in current European Organisation for Research and Treatment of Cancer (EORTC) guidelines [5]. EORTC guidelines are based on a literature review of clinical trial data and under-reporting of febrile events has been noted to be common in randomised controlled trials [17]. This study is the first multi-centre investigation of neutropenic event incidence in general populations of HL patients treated with ABVD. Three retrospective single-centre studies have also addressed this topic [18-20]. Populations studied were similar to ours with respect to median age and grade 3/4 CIN risk per patient. However, grade 3/4 CIN risk per patient was not available from Evens et al. [18], and in the single-physician experience (with no CSF use) reported by Boleti and Mead, the proportion of stage III-IV patients was only 13% [19]. Overall FN incidence was 10%, 5-9% and 5% in the studies by Chand et al. (N = 81) [20], Evens et al. (N = 84) [18] and Boleti and Mead (N = 38) [19], respectively. These findings are not incompatible with our results, considering that retrospective data may be affected by incomplete recording. In addition, practice patterns can differ, and chance effects may play a role in small patient samples.

In both the US and EU populations, chemotherapy delivery was suboptimal with 18-22% of patients receiving RDI ≤ 85% compared to standard/planned. As the importance of ABVD dose intensity in determining remission and survival has not yet been defined [2], the clinical impact of this suboptimal ABVD delivery is not known. However, the data highlight that impaired chemotherapy delivery remains a problem in everyday clinical practice, although single centres may achieve very high average chemotherapy dose intensity [18]. Univariate analysis showed that grade 4 CIN increased the risk of dose delays > 3 days; however, the small patient numbers in each data set did not allow for efficient

multivariate adjustment to assess the link between neutropenia and compromised chemotherapy delivery. Moreover, due to incomplete timing information, we could not clearly establish which dose delays and dose reductions occurred before or after neutropenic events, which may have diluted some associations. The influence of reduced or delayed chemotherapy delivery on neutropenic event occurrence remains to be assessed in HL patients receiving ABVD.

Use of primary CSF prophylaxis in ABVD patients was more common in the US than the EU, and in the univariate analysis performed, CSF prophylaxis was associated with a reduced risk of grade 4 CIN. However, the numbers of patients in each dataset were too small for efficient multivariate analysis of CIN risk. Despite greater CSF use and more dose reductions in the US population, similar FN rates were observed between patients in the EU and the US. This may be explained by a more advanced disease state in US patients, which has been identified as an adverse risk factor for increased incidence of FN [5].

In summary, CIN was frequent and FN occurrence clinically relevant in HL patients receiving ABVD chemotherapy. Dose delays and dose reductions were frequent and resulted in suboptimal delivery of chemotherapy in approximately one fifth of patients. Use of primary CSF prophylaxis was more common in the US than the EU and appeared to reduce CIN rates.

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Authors' contributions

RP, MS and TDS were involved in the collection and interpretation of INC-EU prospective study data. EC and GHL were involved in the collection and interpretation of ANC prospective study data. MS performed the data analysis presented here. RP, MS, TDS, EC and GHL participated in drafting the manuscript. All authors read and approved the final manuscript.

Authors Information

MS, RP, and TDS: On behalf of the Impact of Neutropenia in Chemotherapy - European Study Group (INC-EU).

EC and GHL: On behalf of the Awareness of Neutropenia in Chemotherapy Study Group (ANC)

Competing interests

RP has received honoraria from Amgen, Bayer and Roche and has been a paid expert for Amgen, Bayer and Roche.

MS has received honoraria and research funding from Amgen and has acted as a consultant for Amgen.

GHL has been a PI on a research grant from Amgen to the Duke University in support of the ANC Study Group and has received honoraria from Amgen.

EC and TDS have no competing interests.

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