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Patterns of Growth Factor Usage and Febrile Neutropenia Among Older Patients with Diffuse Large B-Cell Non-Hodgkin Lymphoma Treated with CHOP or R-CHOP: The Intergroup Experience (CALGB 9793; ECOG-SWOG 4494)

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Abstract

Patterns of myeloid growth factor (GF) usage and febrile neutropenia (FN) were examined in patients >60 years of age with diffuse large B-cell non-Hodgkin lymphoma (DLBCL) enrolled on CALGB 9793/ECOG-SWOG 4494, receiving initial therapy with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or rituximab+CHOP (R-CHOP). Myeloid GFs were administered to 256/520 (49%) patients. Indications for use were: prevent dose reduction/dose delay (81%, 207/256); treat FN or nonfebrile neutropenia (19%, 48/256). One or more FN episodes occurred in 41% (212/520) of patients, with FN most often in cycle 1 (38% of episodes). In multivariate analysis, risk factors for FN included age >65 years (OR=2.6, 95% CI:[1.4,4.9]) and anemia (hemoglobin <12 g/dl) (OR=2.2, 95% CI:[1.4,3.5]. Myeloid GF use was common in this older DLBCL population receiving CHOP-based therapy, as was FN, especially during cycle one. Risk factors predictive for FN should be used prospectively to identify patients for whom myeloid GFs are best utilized.

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Introduction

The use of anthracycline-based combination chemotherapy to treat diffuse aggressive non-Hodgkin lymphoma (NHL) in older patients is complicated by the frequent occurrence of neutropenia, febrile neutropenia (FN), and serious infections.[1–3] In addition, resulting dose reductions or delays could potentially impact treatment outcome. The frequency of and specific indications for myeloid growth factor (GF) usage had not been well-studied systematically in the era following adoption of the American Society of Clinical Oncology (ASCO) guidelines.[4,5] In an effort to balance optimal outcome with economic considerations, it would be valuable to identify patient subsets in which these agents may be best utilized. A US Intergroup Trial of patients ≥60 years of age with diffuse aggressive NHL (predominantly diffuse large B-cell non-Hodgkin lymphoma [DLBCL]) provides the opportunity for an analysis of GF utilization and FN, both of which are common in this population. Risk factors predictive of FN may also be identified, and used to identify high risk patients for whom GF support is best utilized.

Patients and Methods

The United States Intergroup Trial (CALGB 9793/ECOG-SWOG 4494) for therapy of previously untreated patients ≥60 years of age with diffuse aggressive B-cell non-Hodgkin's lymphoma was open for accrual from December 1997 through July 2001. Additional eligibility criteria included: demonstration of CD20 expression, Ann Arbor stage I–IV measurable disease, ECOG performance status (PS) 0–3, left ventricular ejection fraction ≥45%, adequate renal and hepatic function, absolute neutrophil count (ANC) >1500/mm^3, and platelet count >100,000/mm^3. After signed informed consent, patients were randomized to therapy with either: cyclophosphamide, 750 mg/m^2 intravenously (IV), doxorubicin 50 mg/m^2 IV, vincristine 1.4 mg/m^2 (maximum, 2.0 mg) IV, all Day 1, and prednisone, 100 mg/m^2/day orally Days 1–5 (CHOP), or CHOP plus rituximab, 375mg/m^2 IV, administered seven and three days prior to cycle 1, and two days prior to cycles 3, 5 and 7 (R-CHOP). Patients were restaged after four, six, and eight cycles of therapy. Patients responding to induction therapy (CR, PR) underwent a second randomization to observation or maintenance rituximab, 375mg/m^2 IV weekly X4, repeated every six months for two years. The primary outcomes of this study have been previously reported.[6,7]

Protocol guidelines were provided for therapy-related myelosuppression. If Day 1 ANC was <1500 cells/mm^3, treatment was delayed a week. If FN occurred in the prior treatment cycle, cyclophosphamide and doxorubicin doses were reduced by 50% in the next cycle. These doses could be increased by 25% if the subsequent cycle was well tolerated, with no grade 3/4 hematologic toxicities. Myeloid GFs (granulocyte colony stimulating factor [G-CSF], granulocyte-macrophage CSF [GM-CSF]) were not allowed with the first treatment cycle. ASCO GF guidelines were to be followed thereafter, including GF use to maintain dose intensity in event of neutropenic fever or dose reduction/delay.[5] Prophylactic antimicrobial therapy usage was at the discretion of the treating physician.

Case report forms of all enrolled study patients were reviewed, with data compiled in a collection tool and added to the study database. Data from the maintenance treatment period

were not assessed for this analysis. A separate data collection form for each cycle of induction chemotherapy included body surface area (BSA), delivered doses of each agent, and date of Day 1. The timeliness of cycle administration (i.e., every 21 days) was recorded, or if treatment was delayed, the number of days. Any use of myeloid GF (G-CSF, GM-CSF) was reported, and if so, which cycle days and duration of administration. Reasons for usage were: 1) treatment for FN, 2) treatment for non-febrile neutropenia (NFN) (nadir ANC $\leq 1000/mm^3$ with no fever), 3) hospitalization for FN in a prior cycle, or 4) to prevent dose reduction/dose delay. For purpose of the primary study analysis, myeloid GF usage was defined as use of either G-CSF or GM-CSF to prevent dose reduction/delay, or as prophylaxis for a prior FN hospitalization, given within Days 1–6 of the treatment cycle.

Data were also collected on the occurrence of neutropenia (defined as $<1000/mm^3$ neutrophils plus bands), and characterized by the Common Toxicity Criteria grading scale. It was assessed by cycle if the patient had FN (defined as fever of $\geq 38.3^0$ C, with ANC $\leq 1000/mm^3$) or NFN. Also collected was the nadir cycle day, number of days ANC$<1000/mm^3$, hospitalization and length of stay for FN, and the use, if any, of oral prophylactic antimicrobial agents.

Objectives

The study was designed to assess myeloid GF usage and occurrence of FN in an older patient DLBCL population receiving initial CHOP or R-CHOP therapy. Frequency of and indications for GF usage, and incidence and risk factors for FN, were retrospectively determined.

Statistical Considerations

Descriptive statistics were provided for baseline characteristics. Two-sided Fisher's exact tests were used to assess associations between each risk factor and GF usage, as well as FN incidence.[8] To evaluate the correlation of GF usage with patient characteristics, the primary endpoint for analysis is the proportion of patients whose indication for GF use was either to prevent dose reduction/dose delay, or as prophylaxis in patients with a prior FN hospitalization, and was given within cycle Days 1–6. Estimated proportions are reported as well as 95% confidence intervals (CI). The time to first FN was also evaluated by baseline characteristics, and differences between risk groups were tested using the log-rank method.[9] The logistic regression model was used to examine associations of risk factors with GF usage or FN incidence,[10] and the Cox proportional hazards model was used to examine associations of risk factors with time to first FN.[11] Adjusted odds ratio (OR), hazard ratio estimates and their corresponding 95% confidence intervals are provided. Hazard rate (HR) of first FN incidence was also plotted using an in-house S-Plus function *hazex*.

Results

A total of 632 patients were enrolled on this trial, of which 267 R-CHOP and 279 CHOP patients were eligible[6]. Among these 546 patients, GF usage data were available for 528 patients, eight of whom received first cycle GF and were excluded from analysis. Baseline

demographics of the 520 eligible patients are detailed (Table 1). The majority of patients were ≥65 years of age, with a favorable PS (0/1). Approximately 60% of patients had a high-intermediate or high International Prognostic Index (IPI) risk score. Oral prophylactic antibiotics were utilized in 7% of cycles.

Myeloid GF Usage

Of the 520 evaluable patients, 256 (49%) received a myeloid GF during therapy. GF used was G-CSF (93%), GM-CSF (5%), or both GF (2%) over various cycles. The median number of cycles for which GF was used was three (range, 1–7). Median duration of GF usage in a cycle was nine days. Overall, GF were used in 520/3216 (16%) cycles of administered chemotherapy. GFs were used to prevent dose reduction/dose delay or because of a prior FN hospitalization in 82%, or for the treatment of either FN or NFN in 18%. The primary study analysis definition of GF usage (GF administration within Days 1–6 of the treatment cycle either to prevent dose reduction/dose delay or as prophylaxis for a prior FN hospitalization) was met in 173/520 patients (33%, 95% C.I. [29,38%]). Among the other 83 patients, the indication for GF was treatment of FN/NFN in 48 (9%), prevent dose reduction/dose delay or as prophylaxis but begun after cycle day 6 in 34 (7%), and unknown for 1 (<1%). Significantly more patients used GF with later cycles of therapy (Figure 1). In cycle 6, 97/431 patients (23%) received GF compared with only 59/506 patients (13%) in cycle 2 ($p < 0.001$). In summary, GF were utilized to prevent chemotherapy dose reduction/dose delay in approximately 60% of patients, and were used for secondary prophylaxis in cycle(s) following FN hospitalization in one third of patients.

GF use was evaluated by patient characteristics and induction therapy. Age ≥65 years and baseline hemoglobin <12 g/dl were identified as significant risk factors in univariate analysis ($p=0.003$ and $p<0.0001$, respectively) (Table 2) and multivariate logistic regression analysis after adjusting for induction therapy, gender, bulky disease, and IPI score ($p=0.003$ and $p<0.0001$, respectively) (Table 3). The estimated OR for GF use is 2.0 (95% CI [1.3,3.3]) for patients ≥65 years of age compared to those <65 years. The estimated OR for GF use is 2.2 (95% CI [1.5,3.3]) for those patients with baseline hemoglobin <12 g/dl compared to those with hemoglobin ≥ 12 g/dl. GF use did not differ by induction regimen ($p>0.8$).

Febrile Neutropenia

Among the 520 patients, 212 (41%) had ≥1 episode of FN with a 95% CI (37,45%); 141 (27%) had ≥1 FN hospitalization, with a median 5 (range, 1–121) day length of stay. Overall, FN occurred in 261/3216 (8%) delivered cycles of therapy. Median time to FN was 11 days; 38% of all FN episodes occurred in cycle one, when GF usage was not allowed per protocol. The hazard for the first FN occurrence was highest during cycle one ($p<0.0001$) (Figure 2).

Patient study entry characteristics were analyzed to identify predictive factors for FN during cycle one, to minimize the impact of subsequent dose reduction/dose delay and GF use. A univariate analysis of cycle one FN suggested that patients of age ≥65 years ($p=0.002$), baseline hemoglobin <12 g/dl ($p=0.0001$), PS 2–3 ($p=0.02$), and elevated lactic

dehydrogenase (LDH) (p=0.02) were risk factors, with a trend for type of induction therapy (16% vs. 22%, p=0.08) and gender (16% vs. 23%, p=0.07) (Table 2). After adjusting for other factors in a multivariate logistic regression model, an increased risk for first cycle FN was observed for patients ≥65 years of age (OR= 2.6, 95% CI [1.4,4.9], p=0.004) and those with baseline hemoglobin <12 g/dl (OR= 2.2, 95% CI [1.4,3.5], p=0.0009) (Table 3). A marginal difference was observed by induction therapy, indicating that CHOP-treated patients may have a higher risk of cycle one FN (OR= 1.5, 95% CI [0.96,2.4], p=0.08). Although significant in univariate analysis, gender and PS were not selected in the logistic model because of their high correlation with IPI score.

Data regarding NFN, as well as duration of any therapy-related neutropenia, are reported (Table 4). In general, any neutropenia was of brief duration. There was no trend in duration of either NFN or FN by cycle of therapy. Older age (≥65 years) was not associated with first cycle NFN incidence (p>0.9).

Discussion

The U.S. Intergroup trial facilitated a large prospective collection of GF usage data in NHL patients ≥60 years of age receiving CHOP-based therapy, such that patterns of GF utilization and FN occurrence could be examined. Overall, GF were used in 16% of treatment cycles, being administered to approximately half the study patients. Prophylactic myeloid GF support has been shown to reduce grade 3/4 neutropenia and infectious complications as FN in older DLBCL patients receiving anthracycline-based regimens.[2,3,12–18] In our trial, GF were used in most patients to deliver full dose therapy on time, with or without a prior FN episode.

Relative delivered dose intensity (RDI) has been reported to have an impact on survival with R-CHOP therapy in multiple series.[19–22] In several retrospective reports, DLBCL patients who received ≤90% average RDI had decreased OS, with progressively increasing RDI being associated with increased OS.[19,20] Others have reported that a lower RDI threshold (i.e., RDI <70) negatively impacts PFS and OS.[23] Maintaining RDI is more challenging with advancing age, due to excessive hematologic toxicities and the occurrence of FN, resulting in dose reductions.[21,22,24–26] Having PS >1 is also associated with decreased RDI, with the use of primary myeloid growth factor prophylaxis having a protective effect.[27]

In the U.S. Intergroup study, we found that age >65 years and hemoglobin <12 g/dl were significantly associated with GF use. Once initiated, GF support continued for a median three cycles of therapy, with median duration of nine days within a cycle. Data on GF usage from the Groupe d'Etude des Lymphomes de l'Adulte (GELA) trial of CHOP or R-CHOP therapy in elderly DLBCL patients are more limited.[28,29] For patients with grade 4 neutropenia or FN, G-CSF was administered during all subsequent treatment cycles. If grade 4 neutropenia occurred despite GF support, cyclophosphamide and doxorubicin doses were decreased by 50% in subsequent cycles. Similar to our findings, GF support was more common with later cycles of therapy, with 37% of patients requiring GF support for cycle four, and 43% for cycle eight.

A second objective of our study was to determine the incidence of FN and ascertain prognostic factors. FN occurred in 41% of our patients, with 38% of all FN episodes occurring during cycle one, and 47% during cycles one and two. This is consistent with prior reports, in which 58% of FN events occurred in cycle one and 74% in the first two cycles of comparable therapy in a primarily community-based population.[30] Variable rates of FN occurrence have been reported since our study.[19,21,27,31–37] In the German trials including younger and older patients, FN rates were up to 50%.[34,35] Choi et al reported a 42% FN incidence with R-CHOP therapy, with 48% of the episodes occurring in cycle 1, similar to our findings.[37] However, FN rates of 22–27% were reported in other series of CHOP/R-CHOP-treated patients, many of whom were over age 60.[19,21,27,33] Interestingly, in a recent report of adults ≥18 years (51% ≥65 years) receiving R-CHOP, FN occurrence rate was 19%, with 9% FN occurrence in cycle 1.[31] However, in both the low (<20%) and high (≥20%) risk FN subgroups, the use of primary myeloid growth factor prophylaxis had little impact on FN occurrence. Lastly in a large series of patients receiving R-CHOP21 and R-CHOP14 therapies, FN rates were 19% and 20%, respectably, with corresponding cycle 1 FN rates of 47% and 30%.[20] Primary myeloid growth factor prophylaxis was used for 36% of R-CHOP21-treated patients, and 84% of those receiving R-CHOP14.

We found that age >65 years and hemoglobin <12 g/dl were independent risk factors of FN during the first cycle. Age >65 years had been previously reported as a risk factor for FN in multiple series, as well as co-morbidities, marrow involvement, baseline neutropenia, hypoalbuminemia, lymphopenia, and planned average relative dose intensity >80%.[30,38–41] In more recent studies, it was (comment in age grp…) found that female, gender, presence of co-morbidities, and marrow involvement were predictive for FN occurrence in multivariate analyses, but age ≥65 yrs and albumin ≤3.5 g/dl were significant only in univariate analysis.[37] In another series, older age, poor PS, baseline hemoglobin <12 g/dl, and lack of myeloid growth factor prophylaxis were associated with FN occurrence in any cycle of therapy.[31] Co-morbidities were not a risk factor, possibly because of correlation with age and PS. Additional risk factors identified in other series include albumin ≤3.5 g/dl, older age, poor PS, advanced stage disease, presence of co-morbidities, low baseline blood counts, and low BSA/BMI.[5,42,43] A trend toward a lower risk of first cycle FN with R-CHOP was observed in our study (OR 1.5, 95% CI [0.95, 2.4]). Theoretically, the greater efficacy of R-CHOP in reducing tumor burden may be responsible for this observation. The relationship of FN to baseline anemia in our study is not readily explained. Anemia was not a surrogate marker for marrow involvement in our series, as the presence of marrow involvement at diagnosis did not predict for FN. However, anemia may be related to reduced marrow reserve or chronic disease in older patients.

R-CHOP therapy has been identified as having an intermediate probability of FN occurrence by the NCCN and EORTC guidelines.[44,45] In these, as well as the ASCO guidelines, primary myeloid GF prophylaxis has been recommended for older DLBCL patients receiving such therapy.[44–47] The use of such primary prophylaxis varies substantially among countries.[31] However, despite decreasing the relative risk of severe neutropenia and FN occurrence, primary GF prophylaxis has no impact on parameters as infection-related mortality, quality of life, and response parameters.[48,49] Even more importantly in recent reports, primary GF prophylaxis has been found not to be cost-effective compared to

secondary prophylaxis in the treatment of older DLBCL patients.[50,51] Primary prophylaxis would be considered favorable only if FN hospitalization costs increased 2.5-fold from the present, the cost of GF were substantially less, and/or first cycle FN risk was >47%.

Since the publication of the initial R-CHOP trials, it has been recognized that not all elderly patients will tolerate this regimen. The use of pre-phase vincristine and prednisone therapy has been advocated, with reduction in induction therapy toxicities.[52] In a recent retrospective report in DLBCL patients at least 80 yrs of age, delivery of standard dose R-CHOP was felt to be unrealistic, and although rituximab use was associated with decreased mortality, one-yr OS was better when anthracycline dose intensity was <85%, versus ≥85%, perhaps related to baseline PS.[53] In contrast, others have reported that therapy without an anthracycline results in shorter DFS as well as less FN.[54] Non-anthracycline regimens including etoposide, as R-CEOP and R-CEPP, may be utilized. Series of dose-reduced R-CHOP therapy have been reported, with better tolerability, fewer adverse reactions, and reasonable outcome parameters.[55–58] Regardless, identification of subgroups at enhanced risk for FN occurrence remains important for optimal myeloid GF utilization. Minimization of myelosuppression and subsequent infectious complications, especially in older patients, not only reduces morbidity and mortality, but also allows delivery of full dose therapy, which impacts disease outcome.

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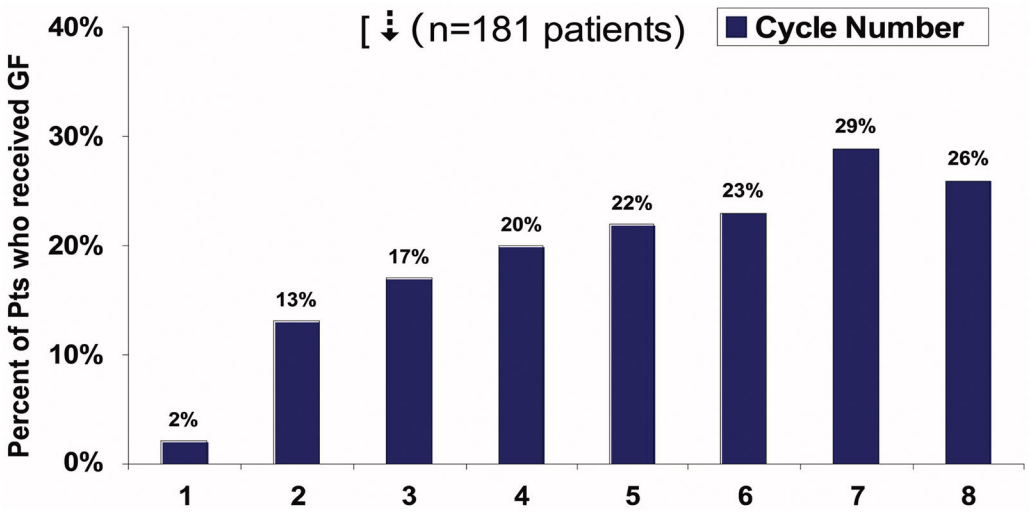

Figure 1.
Myeloid growth factor usage by cycle of therapy.

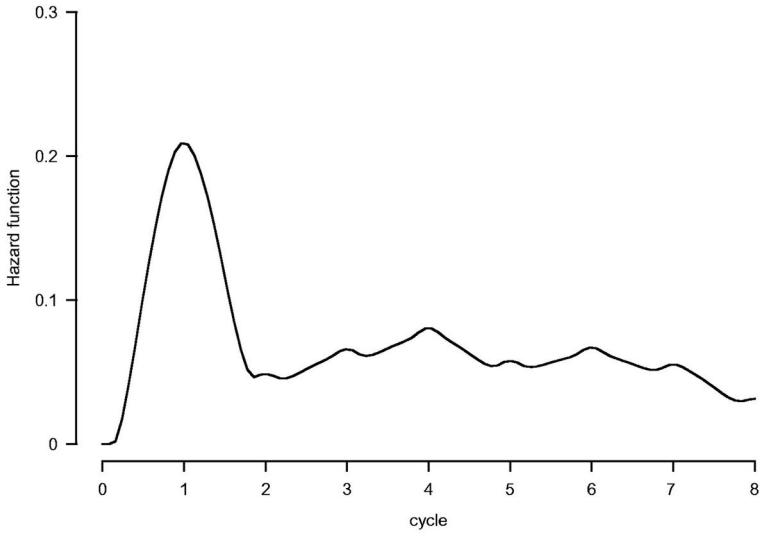

Figure 2.
Hazard of first febrile neutropenia.

Table 1

Patient characteristics

Patient Characteristic	Induction Treatment		All Patients
	R-CHOP (n=250)	CHOP (n=270)	
	N (%)	N (%)	N (%)
Age (yrs)	61(24)	69(26)	130(25)
60–64			
65–69	71(28)	68(25)	139(27)
70–74	58(23)	67(25)	125(24)
75–79	40(16)	47(17)	87(17)
≥ 80	20(8)	19(7)	39(8)
Male gender	130(52)	132(49)	262(50)
ECOG performance status 0–1	216(86)	231(86)	447(86)
Hemoglobin <12 g/dl	96(38)	115(43)	211(41)
Elevated LDH	146(58)	156(58)	302(58)
Marrow involvement	46(18)	52(19)	98(19)
Bulky disease (≥10 cm)	59(24)	53(20)	112(22)
Ann Arbor stage III–IV disease	184(74)	197(73)	381(73)
International Prognostic Index (IPI) group			
Low/Low Intermediate Risk	105(42)	109(41)	214(41)
High Intermediate/High Risk	145(58)	160(59)	305(59)
Age-adjusted IPI group			
Low/Low Intermediate Risk	124(50)	133(49)	257(49)
High Intermediate/High Risk	126(50)	136(50)	262(50)

* LDH, IPI score, and age-adjusted IPI score are unknown for 1 CHOP patient

Table 2

Univariate analysis of growth factor (GF) usage at any cycle* and first cycle febrile neutropenia**

Factor	Level	Number of Patients	Growth Factor		Febrile Neutropenia	
			Use at any cycle N (%)	p-value	Observed in first cycle of therapy N (%)	p-value
Induction treatment	R-CHOP	250	83(33)	0.99	40(16)	0.08
	CHOP	270	90(33)		60(22)	
Age (yrs)	<65	130	29(22)	0.003	13(10)	0.002
	≥65	390	144(37)		87(22)	
Gender	Male	262	79(30)	0.14	42(16)	0.07
	Female	258	94(36)		58(23)	
ECOG performance status	0–1	447	151(34)	0.6	78(17)	0.02
	2–3	73	22(30)		22(30)	
Hemoglobin (g/dl)	<12	211	92(44)	<0.0001	58(27)	0.0001
	≥12	309	81(26)		42(14)	
Lactic dehydrogenase	Normal	217	64(29)	0.13	31(14)	0.02
	Elevated	302	109(36)		69(23)	
Marrow involvement	No	422	137(32)	0.48	78(18)	0.39
	Yes	98	36(37)		22(22)	
Bulky disease (≥10 cm)	No	408	140(34)	0.37	78(19)	0.89
	Yes	112	33 (29)		22(20)	
Ann Arbor stage	I–II	139	44(32)	0.67	29(21)	0.62
	III–IV	381	129(34)		71(19)	
International Prognostic*** Index (IPI) group	Low/LI	305	66(31)	0.34	31(14)	0.02
	HI/High	214	107(35)		69(23)	
Age-adjusted***	Low/LI	257	78(30)	0.16	42(16)	0.10

Factor	Level	Number of Patients	Growth Factor		Febrile Neutropenia	
			Use at any cycle N (%)	p-value	Observed in first cycle of therapy N (%)	p-value
IPI group	HI/High	262	95(36)		58(22)	

*GF use is defined as yes if GF was used either to prevent dose reduction/dose delay, or as prophylaxis in patients with a prior FN hospitalization, and was given within Days 1–6 of the treatment cycle

**Fisher's exact p-value is reported

***LI=Low intermediate

Table 3

Multivariate logistic regression model for growth factor (GF) use * at any cycle and first cycle febrile neutropenia (FN) **

Factor	Reference Group	GF use at any cycle		First cycle FN	
		Estimated odds ratio, 95% CI	p-value	Estimated odds ratio, 95% CI	p-value
Induction treatment	R-CHOP	1.0 (0.7, 1.4)	0.9	1.5 (0.96, 2.4)	0.08
Gender	Male	1.1 (0.7, 1.5)	0.7	1.2 (0.8, 1.9)	0.44
Age (yrs)	<65	2.0 (1.3, 3.3)	0.003	2.6 (1.4, 4.9)	0.004
Hemoglobin (g/dl)	≥12	2.2 (1.5, 3.3)	<0.0001	2.2 (1.4, 3.5)	0.0009
Bulky disease	No	0.8 (0.5, 1.3)	0.3	1.0 (0.6, 1.8)	0.90
IPI score	Low/LI **	1.0 (0.7, 1.5)	0.9	1.4 (0.8, 2.2)	0.21

* GF use is defined as yes if GF was used either to prevent dose reduction/dose delay, or as prophylaxis in patients with a prior FN hospitalization, and was given within Days 1–6 of the treatment cycle

** Wald chi-square p-value is reported

** LI=Low intermediate

Table 4

Incidence and duration of febrile neutropenia (FN) and non-febrile neutropenia (NFN)

Cycle:	Number of patients	Grade 3 or higher Non-Febrile Neutropenia (NFN)			Grade 3 or higher Febrile Neutropenia (FN)		
		Percent of patients	Median (range) duration (days)	Median (range) time to occurrence (days)	Percent of patients	Median (range) duration (days)	Median (range) time to occurrence (days)
1	518	39	2(1–10)	14(8–22)	18	4(1–8)	12(7–18)
2	505	32	1(1–9)	14(2–23)	4	3(1–5)	11(8–16)
3	491	28	1(1–16)	13(2–22)	5	4(1–6)	11(7–22)
4	472	32	1(1–15)	14(1–36)	7	3(1–6)	12(7–16)
5	447	29	1(1–10)	13(1–24)	6	3(1–6)	11(8–17)
6	427	31	2(1–12)	14(7–32)	6	3(1–9)	12(8–16)
7	181	33	1(1–11)	13(1–22)	4	5(1–8)	13(9–15)
8	167	29	1(1–8)	12(1–18)	4	2(1–6)	9(4–15)