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NCCN Clinical Practice Guidelines Panel: Myeloid Growth Factors

Change Request

On behalf of Amgen, I respectfully request that the NCCN Myeloid Growth Factors panel review the enclosed information for revision of the febrile neutropenia (FN) risk category of CHOP and R-CHOP (cyclophosphamide/doxorubicin/vincristine/prednisone/rituximab) for the treatment of non-Hodgkin's lymphoma. Currently, this regimen is categorized as intermediate risk for FN. We at Amgen believe, based on the available published evidence (attached), that the CHOP and CHOP-R regimens for non-Hodgkin's lymphoma should be placed in the high risk category.

Clinical Data

For the purpose of this analysis 15 published studies, prospective, retrospective and observational were reviewed. The overall FN rates were reported in 12 of the studies and ranged from 6.5 to 64% with a median of 39%. Lyman et al. in 2008 reported FN rates of 13.1, 27.9 and 25.1% in non-Hodgkin's lymphoma patients who received primary, secondary prophylaxis, and sub-optimal G-CSF, respectively. In 2016 Morrison et al. reported an FN rate of 41% in an older patient population treated for diffuse large B-cell lymphoma. Two Korean studies published in 2014 reported FN rates of 40.3 and 42.2%. In the Korean studies granulocyte colony stimulating factor (G-CSF) could only be administered if the absolute neutrophil count was less than 1,000 /mcL. Pettengell et al. in 2011 and Salar et al. in 2012 reported FN rates of 47 and 37%, respectively. Primary prophylaxis with G-CSF was administered to 36% of the patients in both studies and in the Salar study 29% of the patients received secondary prophylaxis with G-CSF.

Our review of the data in these studies indicates that the risk of FN exceeds 20% in non-Hodgkin's lymphoma patients being treated with CHOP and R-CHOP. Growth factor support at some level was provided to at least some of the patients in all of the studies, and the rate of FN was lower in those studies where growth factor was used more extensively. Many of the patients received primary and secondary prophylactic G-CSF and others were treated sub-optimally with G-CSF to prevent FN. In the 4 studies referenced by NCCN, the FN rate was at least 15%, despite primary prophylaxis, and the FN rate was higher with secondary prophylaxis. Therefore, we believe, based on the available medical literature that the CHOP and R-CHOP regimens for non-Hodgkin's lymphoma should be placed in the high risk category to assure that patients at high risk for FN receive the appropriate growth factor support.

Respectfully,

Charles Bowers, MD

US Medical, Neupogen/Neulasta

Studies Reporting a High Rate of Febrile Neutropenia

Study	N	FN Rate (%)				G-CSF Use (%)				Study Design	Chemotherapy Regimen
		All	PP	SP	SO	Undefined	PP	SP	SO		
Lee 2012 ⁷	65	60	5				62			Retrospective	CHOP
Pettengell 2011 ¹⁰	702	47					36			Retrospective	RCHOP
Choi 2014 ^{5,*}	181	42				After FN		24		Prospective	RCHOP
Morrison 2016 ¹	520	41				49				Prospective	CHOP/RCHOP
Park 2014 ^{4,*}	397	40				Not routine				Prospective	RCHOP

CHOP, cyclophosphamide + doxorubicin + vincristine + prednisone; FN, febrile neutropenia; PP, primary prophylaxis; RCHOP, rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone; SP, secondary prophylaxis; SO, suboptimal

*Study included a Korean demographic.

Studies with Mixed G-CSF Use

Study	N	FN Rate (%)				G-CSF Use (%)				Study Design	Chemotherapy Regimen
		All	PP	SP	SO	Undefined	PP	SP	SO		
Lyman 2008 ¹¹			13	28	25	Yes				Retrospective	CHOP
Fust 2016 ²	205		4	10	8	Yes				Retrospective	CHOP/RCHOP
Vitolo 2016 ³	200	7	4	10	8		29		70	Prospective	RCHOP
Kikuchi 2014 ⁶	70	16				80				Retrospective	RCHOP
Lugtenburg 2012 ⁸	704	28					45			Observational	RCHOP
Salar 2012 ⁹	1136	37					36	29		Prospective/ Retrospective	RCHOP

CHOP, cyclophosphamide + doxorubicin + vincristine + prednisone; FN, febrile neutropenia; PP, primary prophylaxis; RCHOP, rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone; SP, secondary prophylaxis; SO, suboptimal

Studies Referenced in the NCCN Guidelines

(NCCN Clinical Practice Guidelines in Oncology - Myeloid Growth Factors v1.2017)

Study	N	FN Rate (%)				G-CSF Use (%)				Study Design	Chemotherapy Regimen
		All	PP	SP	SO	Undefined	PP	SP	SO		
Coiffier 2002 ¹⁵	197	64		59						Prospective	CHOP/RCHOP
Lyman 2003 ¹⁴	1355	21		17		92				Retrospective	CHOP/RCHOP
Watanabe 2016 ^{12,*}	149	15					Yes			Prospective	RCHOP
Saven 2006 ¹³	77		15		17	Yes	51		47	Prospective	RCHOP

CHOP, cyclophosphamide + doxorubicin + vincristine + prednisone; FN, febrile neutropenia; PP, primary prophylaxis; RCHOP, rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone; SP, secondary prophylaxis; SO, suboptimal

*Study included a Japanese demographic.

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Note to reader:

A lit search was conducted with the following search terms: CHOP, RCHOP, and Febrile Neutropenia.

Inclusion criteria: All English publications that specified the use of CHOP or RCHOP and provided a % rate of FN.

Exclusion criteria: All publications that did not report FN rate or only reported FN as a hazard ratio.