Neutropenic Risk, Use of Colony Stimulating Factors, and Impact on the Relative Dose Intensity of Administered Chemotherapy

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Background

The relative dose intensity (RDI) is an important predictor of disease-free survival and overall survival in cancer chemotherapy. Specifically, both disease-free and overall survival have been shown to significantly decrease across a variety of tumor types when the delivered RDI falls below 80-85% of the standard regimen.[1-5] The relative dose intensity is also a strong predictor of febrile neutropenia.[6] Conversely, the occurrence of febrile neutropenia is also a predictor of reduced RDI.[7] ASCO and NCCN guidelines recognize the relationship between the two outcomes and recommend the use colony stimulating factors (CSFs) to limit the risk of neutropenia while maximizing the benefit of chemotherapy.[8,9] This study sought to define current practice patterns concerning the management of febrile neutropenia risk by examining the use of prophylactic growth factors and the delivered RDI.

Methods

Data was extracted from the electronic medical records of 945 adult cancer patients treated at a large, 29 center community oncology practice who received a new chemotherapy regimen from January 2007 to February 2009. All patients >18 years of age who had a breast, ovarian, colorectal, lung, and lymphoma primary tumor types were included. Standard regimens were defined using the NCCN Clinical Practice Guidelines applicable to the cancer types investigated and the RDI was estimated using the formula of Lyman and colleagues.[7] If a standard regimen could not be determined, the RDI was assumed to be 100%. Risk of febrile neutropenia was determined using the reported NCCN guideline regimen risk and the logistic regression model of Lyman and colleagues.[8,10] The Wilcoxon-Rank Sum test was used to determine significance between the relative dose intensity of patients receiving primary prophylaxis with CSF.

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Table 1. Descriptive Statistics

	Study Cohort N = 945	
DEMOGRAPHICS	**n**	**%**
Age ≥65 years	334	35.3%
Male Sex	358	37.9%
MEDICAL HISTORY		
Type of Cancer		
Breast	304	32.2%
Colorectal	257	27.2%
NSCLC	191	20.2%
SCLC	44	4.7%
Ovarian	41	4.3%
Lymphoma	110	11.6%
Hx of prior chemotherapy	164	17.4%
CONCOMITANT MEDS		
Immunosuppressives	65	6.9%
Antiemetics	879	93.0%
Primary CSF prophylaxis	329	34.8%
LAB RESULTS		
Elevated Alkaline Phosphatase	187	19.8%
Elevated Total Bilirubin	30	3.2%
Elevated AST	127	13.4%
Glomerular filtration rate (mL/min)		
Mean (SD)	98.1	
Range	15.1-308.1	
CHEMOTHERAPY		
Anthracycline	163	17.2%
Alkylating agents	221	23.4%
Platinum	477	50.5%
Taxane	355	37.6%
Topo. inhibitors type I	92	9.7%
Topo. inhibitors type II	48	5.1%
Gemcitabine	40	4.2%
Vinorelbine	24	2.5%
Planned RDI		
Mean (SD)	87.00%	
Range	2.8%-100%	

Figure 1. RDI Distribution

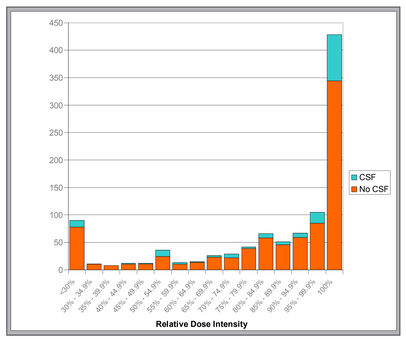

Table 3A. Distribution by NCCN Regimen Risk and CSF Use for Each Cancer Type

	N	Low Risk				Intermediate Risk				High Risk			
		No CSF		CSF		No CSF		CSF		No CSF		CSF	
		n	%	n	%	n	%	n	%	n	%	n	%
Breast	303	116	38.3%	86	28.4%	16	5.3%	38	12.5%	9	3.0%	38	12.5%
Ovarian	41	25	61.0%	11	26.8%	1	2.4%	0	0.0%	3	7.3%	1	2.4%
Colorectal	257	117	45.5%	19	7.4%	91	35.4%	30	11.7%	0	0.0%	0	0.0%
Lymphoma	110	31	28.2%	13	11.8%	17	15.5%	31	28.2%	7	6.4%	11	10.0%
NSCLC	190	37	19.5%	10	5.3%	119	62.6%	24	12.6%	0	0.0%	0	0.0%
SCLC	44	12	27.3%	10	22.7%	10	22.7%	7	15.9%	5	11.4%	0	0.0%

Table 3A. Distribution by Model Risk and CSF Use for Each Cancer Type

	N	Low Risk				Intermediate Risk				High Risk			
		No CSF		CSF		No CSF		CSF		No CSF		CSF	
		n	%	n	%	n	%	n	%	n	%	n	%
Breast	303	62	20.5%	98	32.3%	41	13.5%	23	7.6%	38	12.5%	41	13.5%
Ovarian	41	10	24.4%	11	26.8%	13	31.7%	1	2.4%	6	14.6%	0	0.0%
Colorectal	257	137	53.3%	44	17.1%	19	7.4%	5	1.9%	52	20.2%	0	0.0%
Lymphoma	110	24	21.8%	31	28.2%	12	10.9%	14	12.7%	19	17.3%	10	9.1%
NSCLC	190	97	51.1%	34	17.9%	49	25.8%	0	0.0%	10	5.3%	0	0.0%
SCLC	44	0	0.0%	9	20.5%	3	6.8%	8	18.2%	24	54.5%	0	0.0%

Table 4. Mean and Median RDI by Risk and CSF Use

		Regimen Risk			Model Risk		
		Low	Intermediate	High	Low	Intermediate	High
No CSF	n	338	254	24	330	137	149
	mean RDI	87.8%	84.4%	85.5%	81.2%	92.9%	91.4%
	SD	19.5%	19.4%	24.4%	22.3%	14.5%	13.6%
	median RDI	100.0%	91.8%	100.0%	90.0%	100.0%	100.0%
CSF	n	149	130	50	227	51	51
	mean RDI	87.5%	86.9%	94.7%	83.8%	97.8%	99.1%
	SD	18.9%	22.1%	16.9%	22.5%	5.6%	4.3%
	median RDI	98.8%	99.3%	100.0%	94.9%	100.0%	100.0%
z		*-1.1325*	*2.784*	*-1.5109*	*1.7232*	*1.2875*	*5.0121*
p-value		*0.257*	***0.005***	*0.131*	*0.085*	*0.198*	***<0.001***

Results

Table 1 shows descriptive statistics for this population. In this population, 34.8% of patients received CSFs as primary prophylaxis. The distribution of patients by risk and use of CSFs for each cancer type and overall is displayed in **Table 2**. **Figure 1** shows the distribution of RDI for patients, categorized by whether they received CSF prophylaxis or not. The mean and median RDI administered to patients was 87.0% and 99.0%, respectively. In total, 68.9% of the population received chemotherapy at a RDI ≥ 85%. Patients receiving CSFs had a slight but statistically significant increase in RDI (mean RDI 88.3% vs. 86.3%; z = -2.249; p=0.0246). There was no statistically significant difference in the RDI for patients who developed FN (z = 1.229; p=0.219). **Tables 3a and 3b** show the distribution of patients for each cancer type by level of risk and administration of CSFs. **Table 4** shows that there was no significant difference between the RDI distribution for patients receiving or not receiving CSF prophylaxis when RDI was further stratified by NCCN regimen risk for low (p=0.257 and high (p=0.131) risk patients; however, there was a significant difference in the RDI for intermediate risk patients (p=0.005). When the RDI distribution was stratified by use of growth factor and the Lyman risk model score (**Table 4**), there was no significance difference between the RDI for low (p=0.085) or intermediate risk subjects (p=0.198); however, high risk patients receiving CSFs had significantly higher RDIs (p<0.001) than those who did not receive a CSF.

Discussion

This community-based population of patients receiving systemic chemotherapy received a higher mean RDI than those reported in the medical literature, which may be explained in part by the increased usage of CSF prophylaxis in this population. This study did not consider how the risk of other toxicities impacted the delivered RDI; however, it appears that the risk of FN minimally affected the delivered RDI as the RDI did not significantly decrease in higher risk patients. A large proportion of the patients studied (>30%) received chemotherapy below levels which have been shown to compromise treatment outcomes and more patients had their RDI lowered below 90% (36.5%) than received growth factor. It is possible that some of these patients would have received more curative chemotherapy dosing had a prophylactic CSF been administered. Lack of significance between the RDI of patients receiving and not receiving CSFs when stratified by NCCN high risk regimens suggests that the decision to use CSF prophylaxis is influenced by additional factors. By incorporating these factors, a model-guided strategy could allow for improved categorization of patient FN risk and optimization of RDI through CSF prophylaxis. Further study is needed to validate these findings, ideally in a prospective setting.