Dose Intensity and Hematologic Toxicity in Older Cancer Patients Receiving Systemic Chemotherapy

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BACKGROUND. This prospective study was undertaken to evaluate patient and treatment characteristics that contribute to hematologic toxicity in older cancer patients.

METHODS. A nationwide study of 115 community oncology practices was conducted between 2002 and 2005 with data collected on 976 patients who had received chemotherapy for common malignancies, including lung cancer, colorectal cancer, breast cancer, ovarian cancer, genitourinary cancer, and lymphoma. Primary outcomes included severe neutropenia (SN) and febrile neutropenia (FN). Secondary outcomes included delivered relative dose intensity (RDI) <85%, dose delays ≥15% days, and reductions ≥15%.

RESULTS. Approximately 50% of both patients with early-stage disease and patients with advanced-stage disease received an actual RDI <85%, and this rate reached 60% in the oldest group (aged >80 years). Increasing age was associated with lower actual RDI ($P = .030$) and averaged 87.5% across all elderly age groups. A decreasing trend in SN or FN events occurred with increasing age (P for trend = .039), with the majority of initial neutropenic events occurring in Cycle 1 for all age groups. Among the patients who received an actual RDI ≥85%, there was no significant difference in SN or FN by age group or disease stage. Independent risk factors for the development of SN or FN included cancer type, planned RDI ≥85%, body surface area ≤2m^2, anthracycline- or platinum-based regimens, previous chemotherapy, elevated blood urea nitrogen, and alkaline phosphatase. Neutropenic complications decreased significantly with primary colony-stimulating factor (CSF) prophylaxis (coefficient of determination [R^2] = 0.260; c-statistic = 0.782).

CONCLUSIONS. Among cancer patients aged ≥70 years, 50% of whom received relatively full-dose chemotherapy, increasing age alone did not increase the risk of hematologic toxicity. ***Cancer* 2007;110:1611–20.** © *2007 American Cancer Society.*

KEYWORDS: aging, colony-stimulating factor, dose intensity, dose, neutropenic complications.

It has been established that age-related comorbidities and physiologic changes, such as declining renal and hepatic function and progressive loss of total body protein, increase the risk of chemotherapy-induced toxicity in older cancer patients.[1–3] The effects of age alone on the hematopoietic system, though modest, become more pronounced after age 65.[4] Therefore, not infrequently, age itself is perceived as a risk factor for chemotherapy-induced toxicity. Planned chemotherapy dose reductions that lead to decreased relative dose intensity (RDI) are common, particularly for older patients who are treated with anthracycline-containing regimens for breast cancer or non-Hodgkin lymphoma.[5–7] It has been demonstrated

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that increasing age is an independent risk factor for these substantial reductions in RDI.[8] Dose reductions used as a means of reducing toxicity may undermine outcomes when ≤85% of the standard dose intensity is delivered.[9] Such dose reductions may compromise disease control and overall survival, particularly in patients with potentially curable malignancies.[10,11] Controlled clinical trials have provided limited data on hematologic toxicity and dose intensity of chemotherapy in the elderly. In the current study, we evaluated baseline patient and treatment characteristics that contributed to hematologic toxicity in cancer patients aged ≥70 years who were treated in a community setting.

MATERIALS AND METHODS

Patient Population

A prospective study of 115 community oncology practices in the United States was undertaken between March 2002 and March 2005 that included 976 consecutive patients ages ≥70 years. Stratified random sampling based on practice size and geographic location was used to select sites for participation in this patient registry. All practice sites were approved by institutional review boards, and all patients signed informed consent. Outpatients were enrolled before the initiation of a planned number of cycles of chemotherapy. Pretreatment demographics and clinical characteristics that were gathered on each patient in the first 4 cycles of treatment included age at diagnosis, weight, height, body surface area (BSA), comorbidities, and Eastern Cooperative Oncology Group performance status (ECOG PS). Assessment of comorbidity for each patient was derived from the Charlson Comorbidity Index.[12] We summed the number of comorbidities to derive the variable "≥2 comorbidities." Thus, no weighted measure of disease severity was incorporated into this analysis. Treatment data included chemotherapy regimen and planned dose and schedule as well as information on neutropenic events, including occurrences of severe neutropenia (SN) and febrile neutropenia (FN). Identities of participating patients were kept confidential and inaccessible to investigators through the use of anonymous numeric codes. Major malignancies included lung cancer (27%), colorectal cancer (14%), lymphoma (14%), breast cancer (13%), ovarian cancer (9%), genitourinary cancer (7%), other gastrointestinal cancers (6%), other gynecologic cancers (3%), and head and neck cancers (2%).

Clinical Outcomes

Primary outcome measures included incidence of anemia (hemoglobin <10 g/dL); thrombocytopenia (platelets <75 k/mm^3); SN, which was defined as neutrophils <500 cells/mm^3; and FN (neutrophils <1000 cells/mm^3 and report of fever/infection). In addition, planned RDI and actual RDI, compared with the standard dose intensity for each chemotherapy regimen, were evaluated. Both planned and unplanned reductions in RDI were calculated for each drug and were averaged for each regimen. The standard dose intensity for each drug is defined as the established dose in mg/m^2 per unit time (week). Identifying the standard or established dose intensity involved a comprehensive literature review of articles and chemotherapy reference manuals commonly used by oncologists in the process of selecting chemotherapy.[13–21] If more than 1 possible dosing schedule or dosing interval was identified, oncology experts for each major tumor type were asked to identify the dosing schedule and interval for each regimen that, in their opinion, was considered "standard." Occasionally, when more than 1 potential standard regimen was identified, the more conservative schedule was selected as a means of avoiding overestimation of standards. The RDI for each drug is defined as the ratio of either the actual or planned dose intensity to the standard dose intensity. The RDI for each regimen represents the average RDI for each chemotherapeutic agent in a given regimen. The planned RDI includes dose reductions, as determined by the treating physician, that take effect from the start of treatment. Thus, the planned RDI differs from the standard RDI when such dose reductions are implemented. The difference between the planned RDI and the actual RDI delivered forms the basis for unplanned reductions in RDI and, as such, represents subsequent reductions in dose intensity that were not planned from the start of treatment. Unplanned dose reductions most often are initiated in response to some form of chemotherapy toxicity.

Secondary outcome measurements for the current study included the frequency of actual or planned RDI <85% of the reference standard and the incidence of chemotherapy dose delays ≥15% days and dose reductions ≥15%. Dose reductions and delays are ratios of the actual dose compared with the standard dose and the actual cycle length compared with standard cycle length, respectively.

Colony-stimulating Factors

The frequency and time to the initiation of growth factor use was monitored for every chemotherapy cycle. Ninety-six percent of patients who received growth factor received granulocyte–colony-stimulating factor (G-CSF), and the remaining patients received granulocyte-macrophage–colony-stimulating

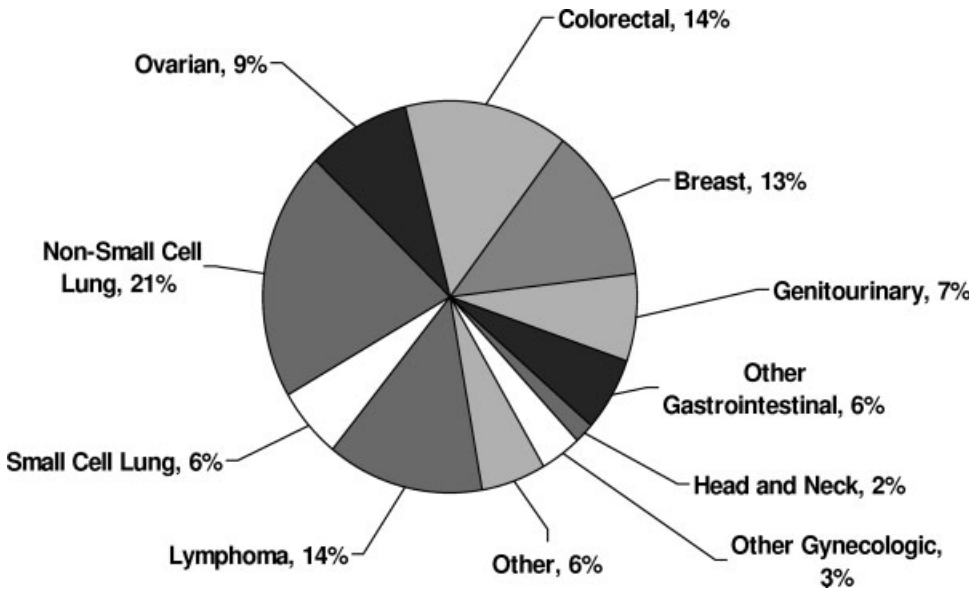

FIGURE 1. The distribution of cancer types in elderly cancer patients (n = 976).

factor. Primary prophylaxis was defined as prophylactic colony-stimulating factor (CSF) administered in conjunction with initiation of the first cycle chemotherapy. All other use of a CSF was considered reactive use. Information on CSF dose and duration of use was not included in this analysis.

Statistical Methods

The distribution of each demographic and clinical variable was calculated using appropriate summary measures. Univariate and multivariate logistic regression analyses were performed to compare the difference among patients ages 70 to 74 years, 75 to 79 years, and ≥80 years. The relation of each demographic and clinical variable with primary and secondary outcomes was assessed using univariate analysis. The chi-square method was used for group comparisons of categorical variables. Trends were evaluated by Cochran-Armitage test. The RDI categorization was based on values <85% or ≥85% for univariate and multivariate analyses. Logistic regression models for outcomes of SN and/or FN and RDI <85% formed the basis of multivariate analyses.

The age groups and cancer categories were included a priori in the models. The additional covariates were considered based on statistical significance and clinical relevance. Global model significance was based on the chi-square method, whereas the significance of individual covariates was based on the Wald statistic. Two-sided tests of the null hypothesis were used throughout. The c-statistic was used to ascertain the multivariate model's level of discrimination. The values of c-statistics range from 0.5 (no discrimination ability) to 1.0 (perfect discrimination).

RESULTS

More than 3500 unselected patients have been enrolled in this prospective registry. We identified 976 patients aged ≥70 years for this analysis with a predominance of lung cancer, breast cancer, and lymphoma (Fig. 1). Forty-four percent of the patients (44%) of were ages 70 to 74 years, 34% were ages 75 to 79 years, and 22% of patients were aged ≥80 years (Table 1).

Approximately half of the patients (51%) had potentially curable, nonmetastatic disease; and the majority (72%) had never received prior chemotherapy. Whereas disease stage and ECOG PS increased with age, the proportion of patients who received previous chemotherapy and the number of comorbidities did not.

SN or FN over the first 4 cycles of chemotherapy occurred in 210 of 930 patients (23%) who had known hematologic toxicity outcomes. The majority of initial neutropenic events occurred in Cycle 1 for all age groups (14%) (Fig. 2). Table 2 summarizes the risk of FN and SN or FN in the first chemotherapy cycles and across all chemotherapy cycles. Baseline elevation in alkaline phosphatase levels, along with anthracycline use, was associated with a significantly increased risk of developing first-cycle FN. In terms of neutropenic events, in all chemotherapy cycles,

TABLE 1
Patient Characteristics, Including Selected Demographics, Treatment-related Factors, and Comorbidities (N = 976)

Characteristic	No. of patients	%
Age, y		
70–74	433	44.4
75–79	329	33.7
≥80	214	21.9
Sex		
Men	439	45
Women	537	55
Stage		
I	67	6.9
II	146	15
III	283	29
IV	468	48
Unknown	12	1.2
ECOG PS		
0	368	37.7
1	451	46.2
2	125	12.8
3	30	3.1
4	2	0.2
Reported BSA >2 m^2	162	16.6
Prior chemotherapy	274	28.1
Anthracycline-containing regimen	160	16.4
Platinum-containing regimen	403	41.3
Taxane-containing regimen	331	33.9
Comorbidities		
Diabetes	174	17.8
Chronic pulmonary disease	123	12.6
Myocardial infarction	57	5.8
Congestive heart failure	45	4.6
Peripheral vascular disease	34	3.5
Cerebrovascular disease	32	3.3
Ulcer	35	3.6
Renal disease	22	2.3
Connective tissue disease	15	1.5
Liver disease	9	0.9

ECOG PS indicates Eastern Cooperative Oncology Group performance status; BSA, body surface area.

anthracycline use and female gender were associated with significantly increased risk. Whereas prophylactic CSF use was not associated with a decreased risk in first-cycle FN, it was associated with a significant reduction in the risk of FN across all cycles ($P = .02$).

A decreasing trend in SN or FN events occurred with increasing age (P for trend = .039). This trend appeared to be driven by the group aged ≥80 years. Although age alone was not associated with any overall significant difference in rates of SN or FN, the SN/FN rate for patients ages 70 to 79 years was 24.2%, and it was 16.7% for patients aged ≥80 years ($P = .022$). Among the approximately 50% of patients who received an actual RDI ≥85%, there was no significant difference in SN or FN by age group or disease stage.

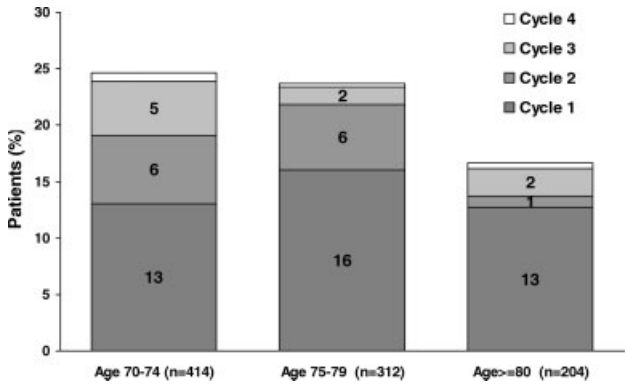

FIGURE 2. Initial episodes of severe or febrile neutropenia in Cycles 1 through 4 by age group (P for trend = .039).

The planned RDI was established in 681 patients based on recognizable regimens, doses, and schedules; whereas the actual RDI was defined in 657 patients. The mean actual RDI was 80% overall, with 336 patients (51.1%) receiving <85% of standard dose intensity. Among 363 older patients with potentially curable, nonmetastatic cancer, 49% received an actual RDI <85%, and 33% of these patients with stage I through III cancers received a planned RDI <85%. Older patients who received a planned RDI <85% maintained an actual RDI <85%. Among patients who began their treatments with a planned RDI ≥85%, an additional 29% decline from baseline RDI in subsequent cycles was observed, with a resultant RDI <85%. Among 556 patients who had an ECOG PS of 0 or 1, 187 patients (33.6%) received a planned RDI <85%. Among patients who had an ECOG PS of 2, 3, or 4, 35 of 101 patients (34.7%) received a planned RDI <85% ($P = .84$). Regarding planned RDI as a function of comorbidity, 192 of 578 patients (33.2%) with 0 or 1 comorbidity received a planned RDI <85%. There was no statistically significant difference between planned RDI in the patients who had few comorbidities compared with the 30 of 79 patients (37%) who had from 2 to 4 comorbidities and received a planned RDI <85% ($P = .40$).

Most of the planned RDI reductions did occur in association with certain types of chemotherapy. Significantly more planned RDI <85% was observed with taxane- and platinum-containing regimens. Significantly less planned RDI <85% was observed with anthracycline-containing regimens compared with nonanthracycline-containing regimens. Table 3 shows both the planned and actual RDI <85% for major clinical variables.

Age ≥80 years was associated with a lower actual RDI ($P = .017$), although the planned RDI did not differ significantly among age groups ($P = .097$), aver-

TABLE 2
Neutropenic Events

		Febrile neutropenia				Febrile or severe neutropenia			
		Cycle 1		All cycles		Cycle 1		All cycles	
Variable	No.	No. (%)	*P*	No. (%)	*P*	No. (%)	*P*	No. (%)	*P*
All patients	930	34 (3.7)		66 (7.1)		130 (14)		210 (22.3)	
Cancer type			.001		<.001		<.001		<.001
Colorectal	126	2 (1.6)		4 (3.2)		9 (7.1)		17 (13.5)	
Small cell lung	55	8 (14.5)		12 (21.8)		21 (38.2)		29 (52.7)	
Nonsmall cell lung	193	4 (2.1)		8 (4.1)		15 (7.8)		27 (14)	
Ovarian cancer	82	3 (3.7)		5 (6.1)		8 (9.8)		16 (19.5)	
Breast cancer	122	5 (4.1)		15 (12.3)		25 (20.5)		38 (31.1)	
Lymphoma	130	6 (4.6)		13 (10)		32 (24.6)		47 (36.2)	
Other	222	6 (2.7)		9 (4.1)		20 (9)		36 (16.2)	
Age, y			.97		.70		.44		.07
70–74	414	15 (3.6)		32 (7.7)		54 (13)		102 (24.6)	
75–79	312	12 (3.8)		22 (7.1)		50 (16)		74 (23.7)	
≥80	204	7 (3.4)		12 (5.9)		26 (12.7)		34 (16.7)	
Female sex	514	23 (4.5)	.14	46 (8.9)	.01	85 (16.5)	.01	137 (26.7)	.001
Education ≤8 grades	100	6 (6)	.19	10 (10)	.23	13 (13)	.77	22 (22)	.88
BSA ≤2 m^2	774	29 (3.7)	.74	58 (7.5)	.29	117 (15.1)	.03	187 (24.2)	.01
ECOG PS 0/1	784	26 (3.3)	.20	53 (6.8)	.35	110 (14)	.92	176 (22.4)	.82
Stage I–III	483	17 (3.5)	.92	40 (8.3)	.09	74 (15.3)	.19	121 (25.1)	.05
No. of comorbidities ≥2	112	6 (5.4)	.31	8 (7.1)	.98	18 (16.1)	.5	22 (19.6)	.43
Prior chemotherapy	265	11 (4.2)	.62	20 (7.5)	.74	47 (17.7)	.03	70 (26.4)	.07
Baseline ANC <3.5 × 10^9/L	195	5 (2.6)	.34	13 (6.7)	.75	33 (16.9)	.19	48 (24.6)	.43
Baseline protein <5.5 g/dL	20	0 (0)	.38	2 (10)	.61	2 (10)	.6	7 (35)	.18
Baseline glucose >120 mg/dL	320	11 (3.4)	.80	18 (5.6)	.21	50 (15.6)	.29	80 (25)	.2
Baseline BUN >20 mg/dL	290	12 (4.1)	.60	18 (6.2)	.48	49 (16.9)	.08	74 (25.5)	.15
Baseline ALP >120 U/L	217	13 (6)	.04	17 (7.8)	.63	39 (18)	.05	56 (25.8)	.19
Anthracyclines	156	11 (7.1)	.01	25 (16)	<.001	53 (34)	<.001	75 (48.1)	<.001
Platinums	383	16 (4.2)	.48	28 (7.3)	.83	51 (13.3)	.63	94 (24.5)	.23
Taxanes	320	8 (2.5)	.17	18 (5.6)	.21	26 (8.1)	<.001	56 (17.5)	.007
Planned RDI, %			.86		.05		.04		.01
≥85	429	17 (4)		40 (9.3)		73 (17)		117 (27.3)	
<85	224	7 (3.1)		12 (5.4)		24 (10.7)		41 (18.3)	
Unknown	277	10 (3.6)		14 (5.1)		33 (11.9)		52 (18.8)	
Planned cycle length ≥4 wk	271	11 (4.1)	.68	18 (6.6)	.72	26 (9.6)	.01	47 (17.4)	.01
Prophylactic CSF	137	2 (1.5)	.14	3 (2.2)	.02	8 (5.8)	.003	23 (16.8)	.08

BSA indicates body surface area; ECOG PS, Eastern Cooperative Oncology Group performance status; ANC, absolute neutrophil count; BUN, blood urea nitrogen; ALP, alkaline phosphatase; RDI, relative dose intensity; CSF, colony-stimulating factor.

aging 87.5% across all elderly age groups (Fig. 3). The average actual RDI decreased to 76% in patients aged ≥80 years, and 82 of those patients (60%) received <85% of the standard dose intensity (Fig. 4). Delays ≥15% and RDI <85% were more common among patients who had stage IV disease compared with patients who had early-stage disease (Fig. 5).

The use of anthracycline-containing regimens was associated with a greater risk of SN or FN compared with nonanthracycline regimens (48% vs. 17%, respectively; $P < .001$). The use of taxane-containing regimens decreased with advancing age (36%, 35%, and 28% for the groups ages 70–74 years, 75–79 years, and ≥80 years, respectively; P for trend = .050). There was no statistically significant difference in the rates of anemia or thrombocytopenia among the different age groups. This was observed in the older patients overall and in the group of patients who received an RDI ≥85%. Disease stage did not alter this finding.

CSF was used in 34% of patients over the first 4 cycles of therapy, including 14% of patients who received CSF prophylactically in Cycle 1. Although the use of primary CSF prophylaxis was greatest among the patients with lymphoma (25%), and the overall use of CSF was greatest in patients with small cell lung cancer (60%) and lymphoma (56%), there were no significant differences in CSF use by age group.

TABLE 3
Relative Dose Intensity

Variable	No.	Planned RDI <85% No. (%)	*P*	Actual RDI <85% No. (%)	*P*
All patients	657	222 (33.8)		336 (51.1)	
Cancer type			<.001		<.001
Colorectal	123	33 (26.8)		56 (45.5)	
Small cell lung	52	20 (38.5)		31 (59.6)	
Nonsmall cell lung	184	78 (42.4)		119 (64.7)	
Ovarian	78	35 (44.9)		41 (52.6)	
Breast	114	23 (20.2)		36 (31.6)	
Lymphoma	106	33 (31.1)		53 (50)	
Age, y			.30		.03
70–74	305	102 (33.4)		155 (50.8)	
75–79	216	67 (31)		99 (45.8)	
≥80	136	53 (39)		82 (60.3)	
Female sex	389	130 (33.4)	.81	189 (48.6)	.11
Education ≤8 grades	79	38 (48.1)	.004	57 (72.2)	<.001
BSA ≤2 m^2	554	186 (33.6)	.79	280 (50.5)	.48
ECOG PS 0/1	556	187 (33.6)	.84	281 (50.5)	.47
Stage I–III	363	118 (32.5)	.37	177 (48.8)	.15
No. of comorbidities ≥2	79	30 (38)	.40	45 (57)	.23
Prior chemotherapy	185	70 (37.8)	.16	101 (54.6)	.26
Baseline ANC <3.5×10^9/L	133	44 (33.1)	.80	62 (46.6)	.20
Baseline protein <5.5 g/dL	13	7 (53.8)	.12	11 (84.6)	.01
Baseline glucose >120 mg/dL	223	86 (38.6)	.06	127 (57)	.03
Baseline BUN >20 mg/dL	189	68 (36)	.45	102 (54)	.36
Baseline ALP >120 U/L	136	49 (36)	.54	73 (53.7)	.51
Anthracyclines	124	27 (21.8)	.002	49 (39.5)	.004
Platinums	261	108 (41.4)	.001	159 (60.9)	<.001
Taxanes	216	89 (41.2)	.005	121 (56)	.08
Planned RDI, %					<.001
≥85				125 (28.7)	
<85				211 (95)	
Planned cycle length ≥4 weeks	186	110 (59.1)		123 (66.5)	<.001
Prophylactic CSF	99	30 (30.3)	.43	43 (43.4)	.10

BSA indicates body surface area; ECOG PS, Eastern Cooperative Oncology Group performance status; ANC, absolute neutrophil count; BUN, blood urea nitrogen; ALP, alkaline phosphatase; RDI, relative dose intensity; CSF, colony-stimulating factor.

In multivariate analysis, the risk of SN or FN increased significantly with cancer type (particularly for patients with lung cancer, breast cancer, and lymphoma), planned RDI ≥85%, BSA ≤2 m^2, anthracycline- or platinum-based regimens, previous chemotherapy, elevated blood urea nitrogen (BUN), and elevated alkaline phosphatase. The risk of neutropenic complications decreased significantly with primary CSF prophylaxis (coefficient of determination [R^2] = 0.260; c-statistic = 0.782) (Table 4).

Multivariate analysis of actual RDI <85% over Cycles 1 through 4 was limited to patients aged ≥70 years with lymphoma, lung cancer, breast cancer, ovarian cancer, or colorectal cancer (n = 741 patients). Among those patients, 657 (89%) received

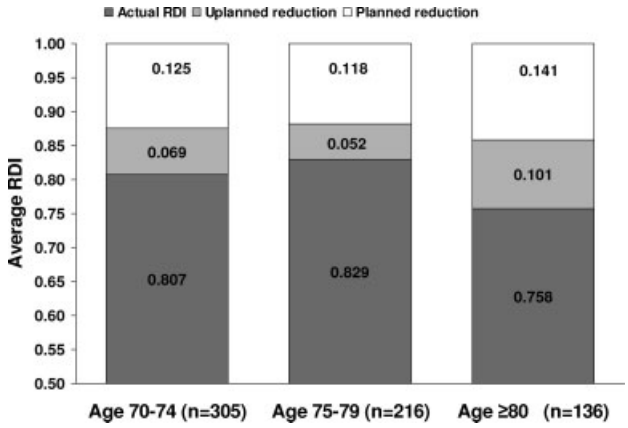

FIGURE 3. The average relative dose intensity (RDI) is illustrated by age group.

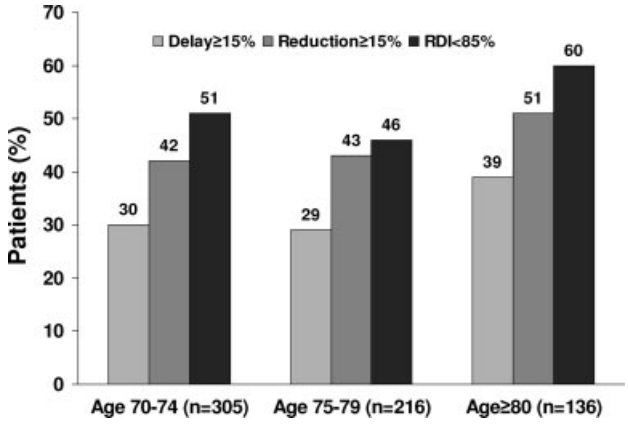

FIGURE 4. Dose reductions/delays and actual relative dose intensity (RDI) <85% are illustrated by age group.

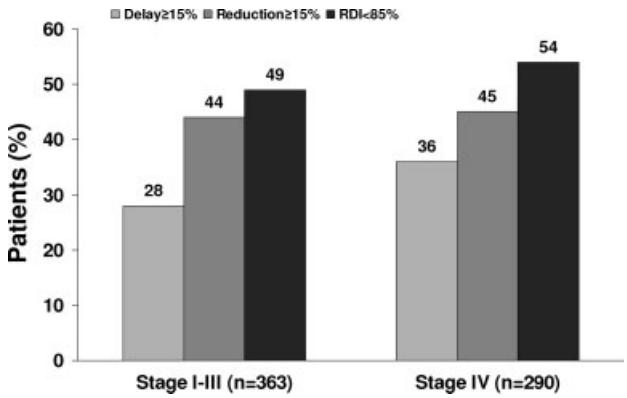

FIGURE 5. Dose reductions/delays and actual relative dose intensity (RDI) <85% are illustrated by group according to disease stage. Patients with unknown stage were not included in the calculations for this chart.

TABLE 4
Multivariate Logistic Regression Model for Severe or Febrile Neutropenia Over Cycles 1 Through 4 in Cancer Patients Aged ≥70 Years (n = 928)*

Variable	OR (95% CI)	*P*
Cancer type		<.0001
Colon	1.35 (0.52–3.52)	.5373
Lung small cell	7.26 (2.82–18.74)	<.0001
Lung nonsmall cell	0.92 (0.38–2.20)	.8468
Ovary	1.01 (0.39–2.63)	.9783
Breast	2.76 (1.10–6.92)	.0299
Lymphoma	3.36 (1.41–8.02)	.0063
Other tumors	1.00	—
Age, y		.1414
70–74	1.63 (0.99–2.67)	.0546
75–79	1.55 (0.93–2.59)	.0815
≥80	1.00	—
Planned RDI, %		.0794
<85	1.00	—
≥85	1.69 (1.06–2.67)	.0263
Unknown	1.64 (0.77–3.52)	.2009
Anthracycline-based regimen	6.30 (3.76–10.57)	<.0001
Platinum-based regimen	3.84 (2.34–6.31)	<.0001
BSA ≤2 m^2	1.91 (1.13–3.26)	.0167
Previous chemotherapy	1.87 (1.27–2.77)	.0016
Elevated BUN	1.52 (1.05–2.21)	.0272
Elevated ALP	1.60 (1.07–2.41)	.0264
Prophylactic CSF	0.36 (0.21–0.62)	.0002

OR indicates odds ratio; 95% CI, 95% confidence interval; RDI, relative dose intensity; BSA, body surface area; BUN, blood urea nitrogen; ALP, alkaline phosphatase; CSF, colony-stimulating factor.
* The results were adjusted for an Eastern Cooperative Oncology Group performance status ≥2 and for ≥2 comorbidities, neither of which was statistically significant (model coefficient of determination = 0.26; c-statistic = 0.782).

TABLE 5
Multivariate Logistic Regression Model for Actual Relative Dose Intensity <85% Over Cycles 1 Through 4 in Cancer Patients Aged ≥70 Years (n = 657)*

Variable	OR (95% CI)	*P*
Cancer type		.1096
Lung small cell	1.43 (0.68–2.00)	.3480
Lung nonsmall cell	1.66 (0.98–2.80)	.0603
Ovary	1.04 (0.56–1.94)	.9054
Breast	0.79 (0.44–1.40)	.4136
Lymphoma	1.46 (0.83–2.58)	.1880
Colorectal	1.00	—
Education ≤8 grades	2.55 (1.47–4.44)	.0009
Age, y		.0266
70–74	0.67 (0.43–1.04)	.0760
75–79	0.53 (0.33–0.84)	.0071
≥80	1.00 (Reference)	—
Cycle length, wk	2.63 (1.77–3.89)	<.0001
Platinum based regimen	1.92 (1.20–3.07)	.0064
Reduced protein	6.41 (1.36–30.28)	.0191
Elevated glucose	1.45 (1.01–2.06)	.0418

OR indicates odds ratio; 95% CI, 95% confidence interval.
* The results were adjusted for an Eastern Cooperative Oncology Group performance status ≥2 and for ≥2 comorbidities, neither of which was statistically significant (model coefficient of determination [R^2] = 0.17; c-statistic = 0.701).

a recognized standard regimen, which allowed us to calculate the actual RDI. Table 5 shows that significant predictors of greater reduction in RDI in multiple logistic regression analyses include a lower level of education, the use of a platinum-based regimen and regimens with longer cycle duration, and abnormal baseline glucose and protein levels. Significant predictors of decreased reduction in RDI included age (R^2 = 0.174; c-statistic = 0.701).

The 5 most common reasons for not completing the study included 1) disease progression that necessitated a change in treatment regimen (11%), 2) disease progression with subsequent discontinuation of chemotherapy (10.7%), 3) death as a result of progressive disease (9.1%), 4) any chemotherapy-related toxicity with resultant discontinuation of chemotherapy (8.7%), and 5) hospitalization. In all, 42% of patients in this study did not complete a full 4 cycles of chemotherapy. Among those patients, 44% had stage I through III disease, and 56% had stage IV disease. With respect to age, for the groups ages 70 to 74 years, 75 to 79 years, and ≥80 years, the drop-out rates were 39%, 45%, and 45%, respectively. In terms of the planned RDI, 40% of patients in the group that received a planned RDI ≥85% did not complete 4 cycles of chemotherapy; likewise, 45% of patients who received a planned RDI <85% and 45% of patients for whom the planned RDI was unknown did not complete the study.

DISCUSSION

This report represents one of the largest prospective studies to date of older cancer patients receiving systemic chemotherapy. In approximately 50% of the patients who were treated with relatively full-dose-intensity chemotherapy, increasing age alone did not appear to increase the risk of hematologic toxicity. Nevertheless, fully half of the elderly patients in this study who had common malignancies and were treated with standard regimens experienced major reductions in actual dose intensity, including patients with nonmetastatic, potentially curable malignancies. Thirty-seven percent of patients with stage I through III cancers in this study did not complete treatment, primarily because of disease progression, and 45% of the patients who did not complete treatment received a planned RDI <85%. The potential for compromised outcomes, including decreased sur-

vival, as a result of significant reductions in RDI does not justify the objective of minimizing chemotherapy-induced toxicity, particularly in patients who have responsive and potentially curable malignancies. Others have observed that the benefits of adjuvant chemotherapy are similar for patients aged <70 years compared with patients aged ≥70 years.[22,23] A mortality reduction of almost 15% has been associated with the use of adjuvant chemotherapy in selected older patients with breast cancer.[23]

In this elderly patient population, reductions in planned RDI were associated with decreased rates of neutropenic events, the significance of which was greater over the course of 4 cycles of chemotherapy compared with the initial cycle. These chemotherapy dose reductions, therefore, may be perceived as necessary to avoid incurring neutropenic complications. If no alternative existed to circumvent these hematologic toxicities, then the argument to reduce the dose at the expense of possible compromise in long-term outcome may be justified. However, CSF, which can mitigate neutropenic complications, was administered prophylactically to only 14% of the patients in this study. Despite this, prophylactic CSF in the current study was a statistically significant predictor of reduced neutropenic events. The benefit of prophylactic CSF in terms of abrogating first-cycle FN may have been underestimated because of the limited use of this agent; nevertheless, the association between decreased rates of FN in subsequent chemotherapy cycles was significant. Furthermore, because the planned RDI did not differ significantly among the older age groups, and a trend toward decreasing neutropenic complications was observed with increasing age, the decision to reduce the dose of chemotherapy for most of these patients was made presumably in reaction to toxicity. Randomized controlled trials have demonstrated a significant reduction in the risk of neutropenic complications for older cancer patients in the setting of CSF use.[24–26] Neutropenic complications, thus, may have been reduced further in this study through the more judicious use of CSF.[27] In the 42% of patients who did not complete this study, the rationale was based on factors pertaining to disease progression as opposed to toxicity. Whether disease progression in this study was the result of substantial dose reductions or of fundamentally chemotherapy-resistant disease is unknown.

Independent risk factors for SN or FN among elderly cancer patients in this study included the type of cancer, the type and dose intensity of chemotherapy, BSA ≤2 m^2, previous chemotherapy, and baseline elevations in BUN and alkaline phosphatase. Prophylactic CSF significantly reduced the risk of SN or FN. An ECOG PS ≥2, ≥2 comorbidities, and age were not statistically significant risk factors for the development of SN or FN during chemotherapy. We postulate that the lack of correlation between ECOG PS or comorbidity and neutropenia can be ascribed, at least in part, to variations in chemotherapy regimens, because less myelosuppressive agents may have been selected for sicker patients. Alternatively, our data may lack sufficient sensitivity to detect the real impact of performance status or comorbidity on neutropenia. Planned RDI did not differ significantly between patients who had an ECOG PS ≥2 compared with patients who had an ECOG PS of 0 or 1. Likewise, the planned RDI did not differ significantly between patients with multiple comorbidities and patients with <2 comorbidities. The lack of a perceived significant difference between patients with multiple comorbidities or poor PS and planned RDI, again, may result from insufficient power to detect any real differences. The numbers of patients who had multiple comorbidities and poor functional status were much less than the numbers of healthier patients who had optimal functional status. It is likely that chemotherapy was not recommended as often for more frail, functionally compromised patients.

Independent risk factors for actual RDI <85% included increasing age, chemotherapy cycle length, baseline elevated glucose and reduced serum protein, treatment with a platinum-based regimen, and an education level ≤8th grade. Although the use of anthracycline-containing regimens was a significant predictor of actual RDI ≥85% in univariate analysis, after adjusting for other confounding variables, such as cancer type and increasing age, in the multivariate model, anthracycline use no longer was associated significantly with a reduction in actual RDI.

The finding that a low education level is a highly significant independent risk factor for actual RDI <85% is worthy of note. Others have described socioeconomic variables as predictors of reduced chemotherapy dose intensity.[28] In this study, an education level ≤8 grades may be a surrogate for frailty as a result of possible suboptimal access to adequate healthcare. It also may represent a form of treatment bias on the part of the treating oncologist. Heightened awareness of such prescribing patterns may contribute to optimizing RDI and, consequently, improving outcomes in older patients.

Limitations of this study include the inherent selection bias observed in analyses of observational data. Although we observed no increase in risk of hematologic toxicity in the subgroup of patients who received full doses of chemotherapy, this finding may

have been subject to selection bias. The treating physicians may have selected patients who had a more optimal functional status or fewer comorbidities to undergo treatment with chemotherapy, thus avoiding a recommendation of treatment for less fit older patients. Further selection bias may have been introduced through inconsistency of data submission on consecutive patients. Whereas data submission by participating oncology practices on consecutive patients was encouraged, it was not monitored closely in this study. This form of selection bias falsely may suggest a decreased frequency of reductions in planned and actual RDI, because preselected, more robust, older individuals may be perceived as requiring fewer dose reductions. Furthermore, the actual RDI may have been overestimated given a patient drop-out rate of 42%.

Although the rates of both SN and FN were age- and planned RDI-dependent, no significant difference in the rates of anemia or thrombocytopenia were observed among the different age groups in this study regardless of RDI. These findings support a stronger relation between the planned RDI and effects on the white blood cell neutrophil series compared with the planned RDI and effects on red blood cells or platelets. This may be caused in part by differences in life span between these hematologic cell types. Chemotherapy-related anemia and thrombocytopenia may depend more on the duration of chemotherapy exposure than on the initial chemotherapy dose intensity. Therefore, differences in the rates of chemotherapy-related anemia and thrombocytopenia associated with increasing age may have been underestimated by limiting the study duration to 4 cycles of chemotherapy.

Another limitation of this trial includes the lack of information concerning nonhematologic toxicities, which may have contributed to unplanned reductions in RDI. Again, with only data pertaining to the first 4 cycles of chemotherapy included in this analysis, there may be under-representation of the frequency of nonhematologic toxic events, which are cumulative in the presence of sustained chemotherapy administration. The findings of this study also may under-represent the more widespread problem of under-treatment in this population of patients. Surveillance, Epidemiology, and End Results data from the year 2000 demonstrate that women aged $\geq$70 years with early-stage breast cancer were much less likely to receive adjuvant treatment compared with younger women. Furthermore, only 10% of these older women received an anthracycline-based regimen to treat lymph node-positive, estrogen receptor-negative disease.[29] The influence of age is clearly a factor in the decision of whether or not to recommend chemotherapy to patients. Because, in our study, we evaluated only patients who received treatment, failure by physicians to recommend chemotherapy when indicated solely on the basis of advanced age, thus, is a form of under-treatment that this trial did not address. More randomized clinical trials that include older cancer patients are warranted to assess outcomes as well as patterns of toxicity in this population.

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