Impact of Cumulative Chemotherapy Dose on Survival With Adjuvant FEC-D Chemotherapy for Breast Cancer

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ABSTRACT

Background: Reductions in adjuvant chemotherapy dose <85% for historical regimens (ie, cyclophosphamide/methotrexate/fluorouracil) are known to affect breast cancer survival. This threshold, in addition to early versus late dose reductions, are poorly defined for third-generation anthracycline/taxane-based chemotherapy. In patients with breast cancer receiving adjuvant 5-fluorouracil/epirubicin/cyclophosphamide followed by docetaxel (FEC-D), we evaluated the impact of chemotherapy total cumulative dose (TCD), and early (FEC) versus late (D only) dose reductions, on survival outcomes. **Patients and Methods:** Women with stage I–III, hormone receptor–positive/negative, HER2-negative breast cancer treated with adjuvant FEC-D chemotherapy from 2007 through 2014 in Alberta, Canada, were included. TCD for cycles 1 to 6 of <85% or ≥85% was calculated. Average cumulative dose was also calculated for early (cycles 1–3) and late (cycles 4–6) chemotherapy. Survival outcomes (disease-free survival [DFS] and overall survival [OS]) were estimated using Kaplan-Meier and multivariate analysis. Cohorts were evaluated for uniformity. **Results:** Characteristics were reasonably balanced for all cohorts. Overall, 1,302 patients were evaluated for dose reductions, with 16% being reduced <85% (n=202) relative to ≥85% (n=1,100; 84%). Patients who received TCD ≥85% relative to <85% had superior 5-year DFS (P=.025) and OS (P<.001) according to Kaplan-Meier analysis, which remained significant on univariate and multivariate analyses. In stratified late and early dose reduction cohorts, DFS and OS showed a significant inferior survival trend for dose reduction early in treatment administration in 5-year Kaplan-Meier (P=.002 and P<.001, respectively) and multivariate analyses (hazard ratio [HR], 1.46; P=.073, and HR, 1.77; P=.011, respectively). Dose delays of <14 or ≥14 days and granulocyte colony-stimulating factor use did not affect outcomes. **Conclusions:** Chemotherapy TCD <85% for adjuvant FEC-D affects breast cancer survival. Late reductions (D only) were not shown to adversely affect DFS or OS. Conversely, early reductions (FEC±D) negatively affected patient outcomes.

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Background

Treatment of early-stage breast cancer with adjuvant chemotherapy has improved survival. Landmark meta-analyses by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) initially showed a 20% to 25% relative risk reduction in breast cancer mortality for first-generation regimens (ie, cyclophosphamide/methotrexate/fluorouracil [CMF]) and increased benefit with the addition of anthracyclines and taxanes.¹ Although some meta-analyses have shown the benefits of dose-dense regimens,² others have questioned the appropriateness of comparator arms, citing inferior taxane dosing schedules (paclitaxel given every 3 weeks) as potential confounders.³ Further limiting conclusions are reductions in absolute chemotherapy dose (mg/m²) and cycle delay, shown to affect survival.^{4–7}

Historically, reductions in cumulative dose intensity for chemotherapy (average dose across a given regimen) for first- and second-generation regimens (ie, cyclophosphamide/doxorubicin/5-fluorouracil [CAF], 5-fluorouracil/epirubicin/cyclophosphamide [FEC]) have shown inferior survival in both prospective^{8–10} and select retrospective^{11,12} studies. In a landmark publication, Bonadonna et al⁸ showed superior survival for women receiving ≥85% of the optimal (total cumulative) dose of CMF relative to those receiving <85%. Similar dose–response relationships were shown in the CALGB 8541 trial using CAF.¹³ Further studies aimed at optimizing dose of anthracyclines have shown conflicting data,^{14,15} whereas cyclophosphamide escalation did not lead to improved outcomes.^{16,17} These results are informative but require updating as CMF, CAF, and FEC are inferior to third-generation chemotherapy regimens currently used in the adjuvant setting. Results of retrospective analysis evaluating the effect of chemotherapy dose reduction have been mixed due to a heterogeneity in regimen selection, lack of adjustment for confounding

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variables, and inadequate follow-up to determine effect.^{18,19} Evaluation of docetaxel dose reductions have also yielded conflicting results.^{20,21} Currently, a paucity of data exists for dose adjustments affecting survival for third-generation anthracycline/taxane-based regimens. Furthermore, for sequential regimens, survival effects of early (ie, anthracycline $\pm$ taxane) versus late (taxane only) dose reductions have not yet been fully characterized.

This retrospective study investigated the effect of chemotherapy total cumulative dose (TCD) using historical thresholds of $<85\%$ or $\geq 85\%$ on breast cancer outcomes in women diagnosed with stage I–III, hormone receptor–positive/negative, HER2-negative breast cancer treated with adjuvant FEC for 3 cycles followed by docetaxel (D) for 3 cycles (FEC-D) chemotherapy from 2007 through 2014 in Alberta, Canada. The effects of early (FEC $\pm$ D) versus late (D only) dose reduction were also explored.

Patients and Methods

Study Population and Data Collection

Women diagnosed in 2007 through 2014 with stage I–III, hormone receptor (estrogen receptor [ER] and/or progesterone receptor [PR])–positive or –negative, HER2-negative breast cancer receiving adjuvant FEC-D in Alberta, Canada, were identified using the Alberta Cancer Registry (ACR). Patient inclusion was based on receipt of a minimum of 4 and maximum of 6 cycles of adjuvant FEC-D, with at least 1 cycle of D administered. Patient characteristics (age, menopausal status), pathology (cancer stage according to the 6th edition of the AJCC Cancer Staging Manual [AJCC-6], tumor [T] stage, nodal status, tumor grade, lymphovascular invasion, hormone receptor status), treatment characteristics (surgery type, receipt of granulocyte colony-stimulating factor [G-CSF], chemotherapy cycles), comorbidity score (using the updated Charlson comorbidity index²² [uCCI]), and dose delays (<14 or ≥ 14 days total) were collected from the ACR and through manual chart review where required. This study was approved by the Health Research Ethics Board of Alberta - Cancer Committee.

Chemotherapy Dose Collection and Grouping

Absolute chemotherapy dosages were recorded for individual chemotherapy drugs (ideal body surface area [BSA] dosing: 5-fluorouracil [500 mg/m²], epirubicin

[100 mg/m²], cyclophosphamide [500 mg/m²], docetaxel [100 mg/m²]) and represented as a percentage of the ideal dose (ie, epirubicin % = received dose/ideal dose = [90 mg/m²]/[100 mg/m²] = 90%). The percentage of drug received for individual cycles were weighted equally (ie, F=80%; E=90%; C=90%) and averaged to acquire total dose for individual cycles (ie, total dose for cycle 1 [FEC] = [80% + 90% + 90%]/3 = 86.67%).

TCD Cohorts

Total dose for cycles 1 to 6 were averaged to calculate TCD for the entire FEC-D regimen (Figure 1). If a cycle was missed, a value of 0% was assigned for that cycle and included in the overall TCD calculation. Historical TCD levels of $<85\%$ or $\geq 85\%$ were evaluated. TCD cohorts are outlined in Figure 2A.

Early Versus Late Cumulative Dose Reduction Cohorts

Total dose for FEC cycles 1 through 3 were averaged to calculate early cumulative dose (ECD), and total dose for cycles 4 through 6 were averaged to calculate late cumulative dose (LCD). To explore the potential effects of ECD $\pm$ LCD reduction versus LCD reduction alone, we first considered 3 cohorts: full-dose FEC-D, any FEC $\pm$ any D reduction (ECD), and full-dose FEC (FEC=100%) + any D reduction (LCD). Because survival outcomes for the full-dose and LCD cohorts were equivalent, and those for ECD were inferior to both (supplemental eFigure 1 and eTable 1, available with this article at JNCCN.org), the impact of docetaxel reduction was assessed using the $\geq 85\%$ or $<85\%$ cutpoint for patients who had full-dose FEC and those who had any reduction in FEC. Hence, the final analysis considered 4 cohorts (Figure 2B): FEC $<100\%$ /D $\geq 85\%$ (ECD1), FEC $<100\%$ /D $<85\%$ (ECD2), FEC=100%/D $\geq 85\%$ (LCD1), and FEC=100%/D $<85\%$ (LCD2).

Statistical Methods

Patient, breast cancer, and treatment characteristics were compared using chi-square, Mann-Whitney U, or Kruskal-Wallis H tests where appropriate. For survival calculations, time from definitive breast cancer surgery to last follow-up or event (ie, locoregional or distant recurrence, death) was used. Disease-free survival (DFS) and overall survival (OS) were estimated using the Kaplan-Meier method and compared with log-rank analyses. For the early (ECD1/ECD2) and late (LCD1/LCD2) dose reduction cohorts, the Holm-Sidak method

$$TCD = \frac{([TD \text{ cycle } 1] + [TD \text{ cycle } 2] + [TD \text{ cycle } 3] + [TD \text{ cycle } 4] + [TD \text{ cycle } 5] + [TD \text{ cycle } 6])}{\text{Number of planned cycles } (n=6)}, \text{ where } TD \text{ is total dose}$$

Figure 1. Calculation to determine the total cumulative dose (TCD) for the the FEC-D regimen.

Figure 2. Consort diagram showing creation of (A) TCD cohorts and (B) ECD versus LCD reduction cohorts.

Abbreviations: D, docetaxel; ECD, early cumulative dose; FEC, 5-fluorouracil/epirubicin/cyclophosphamide; LCD, late cumulative dose; OS, overall survival; TCD, total cumulative dose.

was used for pairwise comparison to identify survival differences between groups. To evaluate for potential independent effects of TCD or timing of dose reduction (ECD/LCD) while controlling for known prognostic factors, the Cox proportional hazards model was used. Hazard ratios (HRs) and 95% confidence intervals are reported. For all tests, $P < .05$ was considered significant. Statistics were performed using SigmaPlot V13.0 (Systat Software, Inc.) or SPSS Statistics, version 19 (IBM Corp.).

Results

Patient Eligibility, Selection, and Follow-Up

A total of 1,345 patients were assessed for having received FEC-D chemotherapy in the adjuvant setting; 16 patients were excluded for receiving only the FEC (cycles 1–3) portion of chemotherapy and 27 were excluded for receiving nonstandard regimens (eg, FEC-CMF). A total of

1,302 patients were eligible for allocation in the TCD (Figure 1A) and early (ECD1/2) versus late (LCD1/2) cumulative dose reduction (Figure 1B) analyses. Median follow-up was 59.9 months (range, 6.4–122.0 months).

TCD Cohorts

Patient Characteristics

More patients received chemotherapy TCD ≥85% (n=1,100) versus <85% (n=202) (Table 1), and those with a TCD ≥85% were more likely to be younger (median age, 54 vs 57 years; $P < .001$) and premenopausal (44.5% vs 28.2%; $P \leq .001$), and have a lower number of comorbidities (uCCI score 0; 84.5%) compared with those with a TCD <85% (72.8%).

Of the pathologic features evaluated, only tumor grade was found to be significantly different between cohorts ($P = .014$), with the difference likely due to the higher proportion of grade 1 tumors seen in the TCD

Table 1. Patient Characteristics for TCD Cohorts

Characteristic	TCD $\geq$ 85%	TCD<85%	P Value
	n (%)	n (%)	
Total, N	1,100	202	
Age, y			<.001*
Median	54	57	
Minimum	24	28	
Maximum	75	77	
Menopausal status			<.001*
Premenopausal	490 (44.5)	57 (28.2)	
Postmenopausal	610 (55.5)	145 (71.8)	
AJCC 6 stage			.649
I	17 (1.5)	3 (1.5)	
II	733 (66.6)	128 (63.4)	
III	350 (31.8)	71 (35.1)	
T stage			.126
T1	370 (33.6)	68 (33.7)	
T2	644 (58.5)	109 (54.0)	
T3	85 (7.7)	24 (11.9)	
Unknown	1 (0.1)	1 (0.5)	
Nodal status			.875
N0	93 (8.5)	19 (9.4)	
N1	700 (63.6)	129 (63.9)	
$\geq$ N2	307 (27.9)	54 (26.7)	
Tumor grade			.014*
1	107 (9.7)	7 (3.5)	
2	479 (43.5)	90 (44.6)	
3	512 (46.5)	104 (51.5)	
Unknown	2 (0.2)	1 (0.5)	
Lymphovascular invasion			.126
Absent	413 (37.5)	87 (43.1)	
Present	686 (62.4)	114 (56.4)	
Unknown	1 (0.1)	1 (0.5)	
Hormone receptor status			.204
Positive	942 (85.6)	166 (82.2)	
Negative	158 (14.4)	36 (17.8)	
Surgery			.631
Lumpectomy	429 (39.0)	82 (40.6)	
Mastectomy	671 (61.0)	119 (58.9)	
Unknown	0 (0)	1 (0.5)	
G-CSF			.175
Yes	172 (15.6)	38 (18.8)	
No	907 (82.5)	153 (75.7)	
Unknown	21 (1.9)	11 (5.4)	

(continued)

Abbreviations: AJCC-6, 6th edition of the AJCC Cancer Staging Manual; G-CSF, granulocyte colony-stimulating factor; TCD, total cumulative dose; uCCI, updated Charlson comorbidity index.

*Significant for $P<.05$.

Table 1. Patient Characteristics for TCD Cohorts (cont.)

Characteristic	TCD $\geq$ 85%	TCD<85%	P Value
	n (%)	n (%)	
Chemotherapy cycles			<.001*
4	0 (0)	34 (16.8)	
5	0 (0)	41 (20.3)	
6	1,100 (100)	127 (62.9)	
uCCI score			<.001*
0	930 (84.5)	147 (72.8)	
1	85 (7.7)	31 (15.3)	
≥ 2	85 (7.7)	24 (11.9)	
Dose delay			.777
<14 d	928 (84.4)	172 (85.1)	
≥ 14 d	172 (15.6)	30 (14.9)	

Abbreviations: AJCC-6, 6th edition of the AJCC Cancer Staging Manual; G-CSF, granulocyte colony-stimulating factor; TCD, total cumulative dose; uCCI, updated Charlson comorbidity index.

*Significant for $P<.05$.

$\geq 85\%$ cohort (9.7% vs 3.5%). No significant differences were seen for other pathologic features associated with recurrence risk (ie, hormone receptor negativity, lymphovascular invasion, AJCC-6 stage, large tumors [T3], and nodal status). Additionally, no significant differences were noted for type of surgery performed, receipt of G-CSF, or chemotherapy dose delays of <14 days relative to ≥ 14 days. As expected, receipt of 4 or 5 cycles of chemotherapy was more commonly associated with a TCD <85% ($P<.001$).

Survival Outcomes

Evaluation of TCD thresholds of $\geq 85\%$ versus <85% showed superior DFS at 5 years (85.9% vs 79.2%; $P=.025$) and superior OS at 5 years (88.8% vs 80.7%; $P<.001$) (Figure 3). Inferior DFS for TCD <85% relative to $\geq 85\%$ was seen in univariate analysis (HR, 1.47; $P<.026$) and after correction in multivariate analysis (HR, 1.45; $P=.040$) (supplemental eTable 2). This trend persisted for OS in both univariate (HR, 1.80; $P=.001$) and multivariate analyses (HR, 1.50; $P=.043$) (supplemental eTable 3).

ECD and LCD Cohorts

Patient Characteristics

Most patients were allocated to the FEC=100%/D $\geq 85\%$ group (LCD1; n=791) compared with the FEC=100%/D<85% (LCD2; n=273), FEC<100%/D $\geq 85\%$ (ECD1; n=109), or FEC<100%/D<85% groups (ECD2; n=129). The distribution of early (FEC $\pm$ D) and late (D only) dose

Figure 3. Kaplan-Meier survival curves for 5-year (A) DFS and (B) OS for TCD thresholds of $\geq 85\%$ versus $< 85\%$.

Abbreviations: D, docetaxel; DFS, disease-free survival; FEC, 5-fluorouracil/epirubicin/cyclophosphamide; OS, overall survival; TCD, total cumulative dose.

reductions are shown in Figure 4. Slight differences in age ($P < .001$) and premenopausal status ($P = .002$) were noted between cohorts (Table 2). More patients in the LCD1 cohort had a uCCI score of zero (86.2%) relative to the LCD2 (77.3%), ECD1 (74.3%), and ECD2 cohorts (79.8%) ($P = .002$). No significant differences were seen between pathologic features associated with recurrence risk. With respect to treatment, no significant differences were seen for surgical type or chemotherapy dose delays ≥ 14 days. Slightly more patients received G-CSF in the LCD2 (21.2%) cohort compared with the LCD1 (14.4%), ECD1 (18.3%), or ECD2 cohorts (14.0%) ($P = .033$). As expected, receipt of only 4 or 5 cycles of chemotherapy was

more commonly associated with the LCD2 (8.4% and 10.6%, respectively) and ECD2 cohorts (8.5% and 9.3%, respectively) compared with the LCD1 and ECD1 cohorts (all 0%) ($P < .001$).

Survival Outcomes

DFS was significantly different across the 4 cohorts ($P = .002$; Figure 5A). At 5 years, DFS was higher in the LCD cohorts: 85.5% for LCD1, 87.2% for LCD2, 78.9% for ECD1, and 75.2% for ECD2. OS was also significantly different across the cohorts ($P < .001$; Figure 5B), and was similarly higher at 5 years in the LCD cohorts: 90.0% for LCD1, 87.9% for LCD2, 83.5% for ECD1, and 75.2% for ECD2.

Figure 4. Distribution of (A) early (FEC $\pm$ D) and (B) late (D only) average TCD reductions.

Abbreviations: D, docetaxel; FEC, fluorouracil/epirubicin/cyclophosphamide; TCD, total cumulative dose.

Table 2. Patient Characteristics for Dose Reduction Cohorts

Characteristic	LCD1 (FEC = 100%/D ≥ 85%)	LCD2 (FEC = 100%/D < 85%)	ECD1 (FEC < 100%/D ≥ 85%)	ECD2 (FEC < 100%/D < 85%)	P Value
	n (%)	n (%)	n (%)	n (%)	
Total, N	791	273	109	129	
Age, y					<.001*
Median	54	56	56	55	
Minimum	24	26	27	28	
Maximum	73	73	75	77	
Menopausal status					.002*
Premenopausal	365 (46.1)	93 (34.1)	43 (39.4)	46 (35.7)	
Postmenopausal	426 (53.9)	180 (65.9)	66 (60.6)	83 (64.3)	
AJCC-6 stage					.346
I	12 (1.5)	5 (1.8)	0 (0)	3 (2.3)	
II	539 (68.1)	174 (63.7)	71 (65.1)	77 (59.7)	
III	240 (30.3)	94 (34.4)	38 (34.9)	49 (38.0)	
T stage					.531
T1	276 (34.9)	94 (34.4)	30 (27.5)	38 (29.5)	
T2	456 (57.6)	153 (56.0)	66 (60.6)	78 (60.5)	
T3	59 (7.5)	25 (9.2)	12 (11.0)	13 (10.1)	
Unknown	0 (0)	1 (0.4)	1 (0.9)	0 (0)	
Nodal status					.192
N0	63 (8.0)	19 (7.0)	14 (12.8)	16 (12.4)	
N1	517 (65.4)	176 (64.5)	61 (56.0)	75 (58.1)	
≥N2	211 (26.7)	78 (28.6)	34 (31.2)	38 (29.5)	
Tumor grade					.225
1	79 (10.0)	20 (7.3)	9 (8.3)	6 (4.7)	
2	351 (44.4)	122 (44.7)	39 (35.8)	57 (44.2)	
3	361 (45.6)	130 (47.6)	59 (54.1)	66 (51.2)	
Unknown	0 (0)	1 (0.4)	2 (1.8)	0 (0)	
Lymphovascular invasion					.744
Absent	295 (37.3)	111 (40.7)	43 (39.4)	51 (39.5)	
Present	496 (62.7)	161 (59.0)	65 (59.6)	78 (60.5)	
Unknown	0 (0)	1 (0.3)	1 (1.0)	0 (0)	
Hormone receptor status					.372
Positive	677 (85.6)	236 (86.4)	87 (79.8)	108 (83.7)	
Negative	114 (14.4)	37 (13.6)	22 (20.2)	21 (16.3)	
Surgery					.972
Lumpectomy	309 (39.1)	109 (39.9)	44 (40.4)	49 (38.0)	
Mastectomy	482 (60.9)	163 (59.7)	65 (59.6)	80 (62.0)	
Unknown	0 (0)	1 (0.4)	0 (0)	0 (0)	
G-CSF					.033*
Yes	114 (14.4)	58 (21.2)	20 (18.3)	18 (14.0)	
No	665 (84.1)	204 (74.7)	86 (78.9)	105 (81.3)	
Unknown	12 (1.5)	11 (4.1)	3 (2.8)	6 (4.7)	

(continued on next page)

Abbreviations: AJCC-6, AJCC Cancer Staging Manual, 6th Edition; D, docetaxel; ECD, early cumulative dose reduction; FEC, 5-fluorouracil/epirubicin/cyclophosphamide; G-CSF, granulocyte colony-stimulating factor; LCD, late cumulative dose reduction; uCCI, updated Charlson comorbidity index.

*Significant for $P < .05$.

Table 2. Patient Characteristics for Dose Reduction Cohorts (cont.)

Characteristic	LCD1 (FEC=100%/D≥85%)	LCD2 (FEC=100%/D<85%)	ECD1 (FEC<100%/D≥85%)	ECD2 (FEC<100%/D<85%)	P Value
	n (%)	n (%)	n (%)	n (%)	
Chemotherapy cycles					<.001*
4	0 (0)	23 (8.4)	0 (0)	11 (8.5)	
5	0 (0)	29 (10.6)	0 (0)	12 (9.3)	
6	791 (100)	221 (81.0)	109 (100)	106 (82.2)	
uCCI score					.002*
0	682 (86.2)	211 (77.3)	81 (74.3)	103 (79.8)	
1	55 (7.0)	29 (10.6)	16 (14.7)	16 (12.4)	
≥2	54 (6.8)	33 (12.1)	12 (11.0)	10 (7.8)	
Dose delay					.568
<14 d	661 (83.6)	238 (87.2)	92 (84.4)	109 (84.5)	
≥14 d	130 (16.4)	35 (12.8)	17 (15.6)	20 (15.5)	

Abbreviations: AJCC-6, AJCC Cancer Staging Manual, 6th Edition; D, docetaxel; ECD, early cumulative dose reduction; FEC, 5-fluorouracil/epirubicin/cyclophosphamide; G-CSF, granulocyte colony-stimulating factor; LCD, late cumulative dose reduction; uCCI, updated Charlson comorbidity index.

*Significant for $P<.05$.

Evaluation of DFS in univariate analysis showed a significant, inferior survival trend for early relative to late dose reduction cohorts (ECD1 relative to LCD1: HR, 1.65; $P=.028$; ECD2 relative to LCD1: HR, 1.74; $P=.005$) (Table 3). Although significance was lost in multivariate analysis, survival trends persisted (ECD2 relative to LCD1: HR, 1.46; $P=.073$). Patient characteristics and pathologic features associated with an HR >1.5 and significant effects on DFS in multivariate analysis (Table 3) included uCCI score ≥ 2 relative to 0 (HR, 1.59; $P=.041$), tumor size relative to T1 for both T2 (HR, 2.22; $P<.001$) and T3 (HR, 3.62; $P<.001$), nodal involvement for $\geq N2$ relative to N0 (HR, 2.03; $P=.024$), hormone receptor-negative status relative to hormone receptor-positive (HR, 1.62; $P=.01$), grade 3 histology relative to grade 1 (HR, 3.41; $P=.009$), and lymphovascular invasion present relative to absent (HR, 1.56; $P=.015$). Menopausal status and treatment factors such as G-CSF use and dose delay ≥ 14 days were not shown to affect survival.

Evaluation of OS in univariate analysis also showed a significant inferior survival trend for early relative to late dose reduction cohorts (ECD1 relative to LCD1: HR, 1.92; $P=.012$; ECD2 relative to LCD1: HR, 2.41; $P<.001$) (Table 4). This trend continued in multivariate analysis (ECD2 relative to LCD1: HR, 1.77; $P=.011$). Patient characteristics and pathologic features with an HR >1.5 and significant effects on OS in multivariate analysis (Table 4) included uCCI score ≥ 2 relative to 0 (HR, 2.17; $P=.001$), tumor size relative to T1 for both T2 (HR, 1.77; $P=.011$) and T3 (HR, 3.00; $P<.001$), hormone receptor-negative status relative to hormone receptor-positive (HR, 1.64; $P=.017$), grade 3 histology relative to grade 1 (HR, 7.58; $P=.005$), and lymphovascular invasion

present relative to absent (HR, 1.53; $P=.044$). Nodal involvement $\geq N2$ relative to N0 was significant in univariate analysis (HR, 1.98; $P=.034$) and approached, but did not meet, significance in multivariate analysis (HR, 1.99; $P=.06$). Menopausal status and treatment factors such as G-CSF use and dose delay ≥ 14 days were not shown to affect OS.

Discussion

This study evaluated the impact of chemotherapy dose reduction on breast cancer outcomes for a commonly used third-generation anthracycline/taxane-based regimen. Similar to findings of Bonadonna et al,⁸ cumulative chemotherapy dose $<85\%$ was shown to negatively affect survival in patients treated with FEC-D. This finding supports the notion that even with the addition of taxanes, sustaining total chemotherapy dose $\geq 85\%$ is important for maintaining clinical benefit.

We also evaluated early (FEC±D) relative to late (D only) reductions in chemotherapy dose. Interestingly, worse survival trends were seen in the ECD (FEC $<100\%$ /D $\geq 85\%$ and FEC $<100\%$ /D $<85\%$) versus LCD cohorts (FEC=100%/D $\geq 85\%$ and FEC=100%/D $<85\%$). These data suggest that late reductions in chemotherapy may not have as much of an impact on DFS and OS compared with early reductions. This finding is not completely unexpected, as variability exists in maximally tolerated dose of D, the recommended phase II dose in early-phase clinical trials,^{23,24} and dosing in third-generation regimens (ie, docetaxel/adriamycin/cyclophosphamide [TAC; D=75 mg/m²]²⁵, FEC-D [D=100 mg/m²],²⁶ adriamycin/cyclophosphamide/docetaxel [AC-D; D=75–100 mg/m²]),^{27,28} raising the question of balancing efficacy with toxicity.

Figure 5. Kaplan-Meier curves (top) with Holm-Sidak pairwise comparisons (bottom) for (A) DFS and (B) OS of ECD and LCD cohorts.

Abbreviations: D, docetaxel; DFS, disease-free survival; ECD, early cumulative dose reduction; FEC, fluorouracil/epirubicin/cyclophosphamide; LCD, late cumulative dose reduction; OS, overall survival.

*Significant for $P < .05$.

In the PANTHER study by Foukakis et al,⁷ patients who underwent leukocyte nadir, dose-tailored, adjuvant dose-dense EC-D every 2 weeks (8 cycles) compared with standard 3-weekly FEC-D (6 cycles) chemotherapy were found to have similar 5-year OS rates (92.1% vs 90.2%; $P = .09$), despite the superiority of dose-dense regimens.^{2,3,29} This finding reinforces that lower cumulative dose and early dose reductions likely have a negative impact on survival outcomes.

Our findings highlight the need to avoid chemotherapy dose reductions, particularly early in treatment. Due to the retrospective limitations of our study, it is difficult to accurately evaluate the reasons for dose reduction. Early dose reductions may be related to dose capping for high BSA relating to obesity and concern regarding patient tolerance (ie, comorbidities). Almost one-fifth of the patients in this study had an early dose reduction for the first or subsequent cycles of FEC. In an evaluation of relative dose intensity (RDI) among 190 community oncology practices, Shayne et al³⁰ identified significant predictors of chemotherapy dose reduction, including BSA $> 2 \text{ m}^2$, age ≥ 65 years, febrile neutropenia, and comorbidities (particularly renal disease). In other retrospective studies, obesity has been associated with a

higher likelihood of upfront dose reduction, affecting event-free survival.¹³ In an evaluation of dose-dense chemotherapy tailoring using BSA as a secondary endpoint among patients with breast cancer, Matikos et al³¹ showed improved relapse-free survival relative to standard chemotherapy dosing, but only in obese patients.

We hypothesize that some early dose reductions among our study population were likely related to dose capping, at least before 2012 when ASCO guidelines recommended full weight-based chemotherapy doses in the treatment of obese patients.³² Although our study did not account for BSA or performance status, it was able to examine the impact of comorbidities. Not surprisingly, patients in the LCD1 cohort (FEC=100%/D $\geq$ 85%) had the most favorable comorbidity profile. However, early dose reduction (FEC<100%/D<85% relative to FEC=100%/D $\geq$ 85%) and comorbidity (uCCI > 2 relative to uCCI 0) persisted as significant predictors of worse OS in multivariate analysis.

Early or late dose reductions may be related to toxicity, including febrile neutropenia, and may be associated with dose delay (and consequently lower RDI) with secondary use of G-CSF. Of the entire study population, approximately 16% experienced a dose delay

Table 3. Univariate and Multivariate Analyses for DFS for Dose Reduction Cohorts

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Dose reduction cohorts				
LCD1 (FEC = 100%/D ≥ 85%)	Ref		Ref	
LCD2 (FEC = 100%/D < 85%)	0.840 (0.575–1.226)	.365	0.803 (0.545–1.183)	.267
ECD1 (FEC < 100%/D ≥ 85%)	1.650 (1.054–2.582)	.028*	1.419 (0.888–2.269)	.143
ECD2 (FEC < 100%/D < 85%)	1.744 (1.179–2.581)	.005*	1.458 (0.966–2.200)	.073
Menopausal status				
Premenopausal	Ref		Ref	
Menopausal	1.024 (0.776–1.351)	.867	1.062 (0.794–1.420)	.686
uCCI score				
0	Ref		Ref	
1	1.157 (0.719–1.861)	.548	1.145 (0.704–1.864)	.585
≥ 2	1.625 (1.058–2.495)	.027*	1.592 (1.020–2.486)	.041*
T stage				
T1	Ref		Ref	
T2	2.791 (1.882–4.141)	<.001*	2.223 (1.489–3.325)	<.001*
T3	5.528 (3.393–9.006)	<.001*	3.620 (2.153–6.086)	<.001*
Nodal status				
N0	Ref		Ref	
N1	0.748 (0.434–1.292)	.298	1.160 (0.636–2.115)	.628
≥ N2	1.928 (1.120–3.321)	.018*	2.031 (1.098–3.755)	.024*
Hormone receptor status				
ER+ and/or PR+	Ref		Ref	
ER– and PR–	1.846 (1.326–2.570)	<.001*	1.618 (1.121–2.336)	.010*
Tumor grade				
1	Ref		Ref	
2	2.889 (1.164–7.168)	.022*	1.921 (0.765–4.820)	.164
3	6.057 (2.479–14.799)	<.001*	3.413 (1.366–8.526)	.009*
Lymphovascular invasion				
Absent	Ref		Ref	
Present	2.096 (1.524–2.884)	<.001*	1.560 (1.090–2.232)	.015*
G-CSF				
Yes	Ref		Ref	
No	0.890 (0.615–1.288)	.537	0.926 (0.635–1.350)	.690
Dose delay				
< 14 d	Ref		Ref	
≥ 14 d	0.950 (0.645–1.400)	.796	0.967 (0.651–1.436)	.868

Abbreviations: D, docetaxel; ECD, early cumulative dose reduction; ER, estrogen receptor; FEC, fluorouracil/epirubicin/cyclophosphamide; G-CSF, granulocyte colony stimulating factor; HR, hazard ratio; LCD, late cumulative dose reduction; PR, progesterone receptor; uCCI, updated Charlson comorbidity index.

*Significant for $P < .05$.

of ≥ 14 days. Although we did not specifically calculate RDI (mg/m²/wk), chemotherapy delays (< 14 or > 14 days) did not affect breast cancer survival outcomes in univariate or multivariate analyses. Similarly, of the entire study population, 16% received G-CSF, and use was

not significantly associated with DFS or OS. This interpretation is limited, however, as the reason for G-CSF administration (primary vs secondary prophylaxis) and number of cycles received were not recorded. In early versus late multivariate analysis for OS, nodal status ≥ N2

Table 4. Univariate and Multivariate Analyses for OS for Dose Reduction Cohorts

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Dose reduction cohorts				
LCD1 (FEC=100%/D≥85%)	Ref		Ref	
LCD2 (FEC=100%/D<85%)	1.137 (0.757–1.708)	.536	1.002 (0.657–1.527)	.993
ECD1 (FEC<100%/D≥85%)	1.921 (1.151–3.206)	.012*	1.519 (0.886–2.605)	.128
ECD2 (FEC<100%/D<85%)	2.414 (1.601–3.640)	<.001*	1.774 (1.143–2.753)	.011*
Menopausal status				
Premenopausal	Ref		Ref	
Menopausal	2.108 (1.469–3.023)	<.001*	1.277 (0.912–1.788)	.155
uCCI score				
0	Ref		Ref	
1	1.503 (0.904–2.499)	.117	1.470 (0.871–2.480)	.149
≥2	2.449 (1.602–3.744)	<.001*	2.166 (1.375–3.411)	.001*
T stage				
T1	Ref		Ref	
T2	2.323 (1.513–3.568)	<.001*	1.768 (1.139–2.745)	.011*
T3	5.144 (3.029–8.738)	<.001*	3.004 (1.695–5.324)	<.001*
Nodal status				
N0	Ref		Ref	
N1	0.744 (0.394–1.406)	.363	1.123 (0.555–2.272)	.747
≥N2	1.977 (1.053–3.714)	.034*	1.988 (0.973–4.066)	.060
Hormone receptor status				
ER+ and/or PR+	Ref		Ref	
ER– and PR–	2.168 (1.517–3.100)	<.001*	1.638 (1.094–2.452)	.017*
Tumor grade				
1	Ref		Ref	
2	5.058 (1.229–20.825)	.025*	3.421 (0.820–14.263)	.091
3	12.922 (3.191–52.330)	<.001*	7.584 (1.832–31.404)	.005*
Lymphovascular invasion				
Absent	Ref		Ref	
Present	1.313 (0.954–1.806)	.094	1.531 (1.012–2.316)	.044*
G-CSF				
Yes	Ref		Ref	
No	0.737 (0.495–1.098)	.133	0.796 (0.528–1.198)	.274
Dose delay				
<14 d	Ref		Ref	
≥14 d	1.199 (0.798–1.802)	.382	1.173 (0.771–1.785)	.456

Abbreviations: D, docetaxel; ECD, early cumulative dose reduction; ER, estrogen receptor; FEC, 5-fluorouracil/epirubicin/cyclophosphamide; G-CSF, granulocyte colony-stimulating factor; HR, hazard ratio; LCD, late cumulative dose reduction; PR, progesterone receptor; uCCI, updated Charlson comorbidity index.

*Significant for $P<.05$.

approached but did not reach significance ($P=.060$). This was significant, however, on univariate analysis for OS ($P=.034$) and univariate and multivariate analyses for DFS ($P=.018$ and $.024$, respectively), and may represent low patient numbers in this specific group.

Conclusions

Among women with stage I–III breast cancer treated with the third-generation FEC-D regimen in the adjuvant setting, chemotherapy TCD <85% versus ≥85% affects survival outcomes, and early (FEC±D) relative to late

(D only) reductions in chemotherapy dose may lead to inferior outcomes. Conversely, late reductions in chemotherapy dose appear to have minimal impact on survival. Medical oncologists should strive to deliver full-dose FEC when prescribing adjuvant FEC-D chemotherapy for breast cancer. Prospective evaluation of the optimal dose for D cycles in this regimen is warranted.

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Supplemental online content for:

Impact of Cumulative Chemotherapy Dose on Survival With Adjuvant FEC-D Chemotherapy for Breast Cancer

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eFigure 1: Kaplan-Meier Curves in Full-Dose FEC-D, ECD, and LCD Cohorts

eTable 1: Holm-Sidak Pairwise Comparisons for DFS and OS

eTable 2: Univariate and Multivariate Analyses of DFS

eTable 3: Univariate and Multivariate Analyses of OS

eFigure 1. Kaplan-Meier curves of (A) DFS and (B) OS for full-dose, ECD (any reduction in FEC $\pm$ any reduction in D), and LCD (full-dose FEC + any reduction in D) cohorts.

Abbreviations: D, docetaxel; DFS, disease-free survival; ECD, early cumulative dose reduction; FEC, 5-fluorouracil/epirubicin/cyclophosphamide; LCD, late cumulative dose reduction; OS, overall survival.

eTable 1. Holm-Sidak Pairwise Comparisons of DFS and OS			
	Full Dose	Any FEC $\pm$ Any D Reduction (ECD) P Value	FEC=100% + Any D Reduction (LCD) P Value
DFS			
Full dose	NA	.01*	.186
Any FEC $\pm$ any D reduction (ECD)	NA	NA	NA
FEC=100%, any D reduction (LCD)	NA	<.001*	NA
OS			
Full dose	NA	<.001*	.739
Any FEC $\pm$ any D reduction (ECD)	NA	NA	NA
FEC=100%, any D reduction (LCD)	NA	<.001*	NA

Abbreviations: D, docetaxel; DFS, disease-free survival; ECD, early cumulative dose reduction; FEC, 5-fluorouracil/epirubicin/cyclophosphamide; LCD, late cumulative dose reduction; NA, not applicable; OS, overall survival.

*Significant for $P < .05$.

eTable 2. Univariate and Multivariate Analyses of DFS

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P Value	HR (95% CI)	P Value
TCD				
FEC-D $\geq$ 85%	Ref		Ref	
FEC-D<85%	1.471 (1.048–2.065)	.026*	1.449 (1.017–2.065)	.040*
uCCI score				
0	Ref		Ref	
1	1.157 (0.719–1.861)	.548	1.276 (0.786–2.071)	.325
$\geq$ 2	1.625 (1.058–2.495)	.027*	1.686 (1.082–2.627)	.021*
T stage				
T1	Ref		Ref	
T2	2.791 (1.882–4.141)	<.001*	2.245 (1.501–3.358)	<.001*
T3	5.528 (3.393–9.006)	<.001*	3.856 (2.297–6.473)	<.001*
Nodal status				
N0	Ref		Ref	
N1	0.748 (0.434–1.292)	.298	1.144 (0.629–2.081)	.659
$\geq$ N2	1.928 (1.120–3.321)	.018*	2.146 (1.164–3.956)	.014*
Hormone receptor status				
ER+ and/or PR+	Ref		Ref	
ER– and PR–	1.846 (1.326–2.570)	<.001*	1.672 (1.156–2.419)	.006*
Menopausal status				
Premenopausal	Ref		Ref	
Menopausal	1.024 (0.776–1.351)	.867	1.207 (0.896–1.627)	.216
Age				
$\geq$ 65 y	Ref		Ref	
<65 y	1.596 (0.971–2.621)	.065	2.369 (1.363–4.116)	.002*
Tumor grade				
1	Ref		Ref	
2	2.889 (1.164–7.168)	.022*	1.873 (0.747–4.701)	.181
3	6.057 (2.479–14.799)	<.001*	3.323 (1.332–8.290)	.01*
Lymphovascular invasion				
Absent	Ref		Ref	
Present	2.096 (1.524–2.884)	<.001*	1.620 (1.135–2.311)	.008*
G-CSF				
Yes	Ref		Ref	
No	1.123 (0.776–1.625)	.537	1.062 (0.731–1.544)	.752
Dose delay				
<14 d	Ref		Ref	
$\geq$ 14 d	0.950 (0.645–1.400)	.796	1.014 (0.685–1.503)	.944

Abbreviations: D, docetaxel; DFS, disease-free survival; ER, estrogen receptor; FEC, 5-fluorouracil/epirubicin/cyclophosphamide; G-CSF, granulocyte colony-stimulating factor; HR, hazard ratio; PR, progesterone receptor; TCD, total cumulative dose; uCCI, updated Charlson comorbidity index.

*Significant for $P<.05$.

eTable 3. Univariate and Multivariate Analyses of OS

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P Value	HR (95% CI)	P Value
TCD				
FEC-D $\geq$ 85%	Ref		Ref	
FEC-D<85%	1.795 (1.252–2.573)	.001*	1.491 (1.012–2.196)	.043*
uCCI score				
0	Ref		Ref	
1	1.503 (0.904–2.499)	.117	1.634 (0.969–2.754)	.065
$\geq$ 2	2.449 (1.602–3.744)	<.001*	2.367 (1.506–3.720)	<.001*
T stage				
T1	Ref		Ref	
T2	2.323 (1.513–3.568)	<.001*	1.785 (1.148–2.774)	.01*
T3	5.144 (3.029–8.738)	<.001*	3.407 (1.926–6.028)	<.001*
Nodal status				
N0	Ref		Ref	
N1	0.744 (0.340–1.406)	.363	1.097 (0.544–2.211)	.796
$\geq$ N2	1.977 (1.053–3.714)	.034*	2.096 (1.028–4.273)	.042*
Hormone receptor status				
ER+ and/or PR+	Ref		Ref	
ER– and PR–	2.168 (1.517–3.100)	<.001*	1.709 (1.140–2.561)	.009*
Menopausal status				
Premenopausal	Ref		Ref	
Menopausal	1.313 (0.954–1.806)	.094	1.468 (1.039–2.074)	.029*
Age				
$\geq$ 65 y	Ref		Ref	
<65 y	1.200 (0.726–1.983)	.478	2.122 (1.201–3.749)	.01*
Tumor grade				
1	Ref		Ref	
2	5.058 (1.229–20.825)	.025*	3.297 (0.790–13.751)	.102
3	12.922 (3.191–52.330)	<.001*	7.347 (1.776–30.395)	.006*
Lymphovascular invasion				
Absent	Ref		Ref	
Present	2.108 (1.469–3.023)	<.001*	1.578 (1.046–2.381)	.03*
G-CSF				
Yes	Ref		Ref	
No	1.357 (0.911–2.021)	.133	1.232 (0.821–1.848)	.314
Dose delay				
<14 d	Ref		Ref	
$\geq$ 14 d	1.199 (0.798–1.802)	.382	1.225 (0.807–1.858)	.341

Abbreviations: D, docetaxel; ER, estrogen receptor; FEC, 5-fluorouracil/epirubicin/cyclophosphamide; G-CSF, granulocyte colony-stimulating factor; HR, hazard ratio; OS, overall survival; PR, progesterone receptor; TCD, total cumulative dose; uCCI, updated Charlson comorbidity index.

*Significant for $P<.05$.