Maintaining Dose Intensity of Adjuvant Chemotherapy in Older Patients With Breast Cancer

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MicroAbstract

Suboptimal dose intensity of adjuvant chemotherapy is associated with a poor prognosis in patients with early stage breast cancer. We investigated the relative dose intensity (RDI) of modern adjuvant chemotherapy regimens in patients 65 years and older. An RDI ≥85% was achieved in 177 (63%) of 281 patients included. Better supportive care of risk groups may further optimise RDI.

Abstract

Introduction

Maintaining relative dose intensity (RDI) of adjuvant chemotherapy ≥85% is associated with improved treatment outcomes in early stage breast cancer (ESBC). Increasing evidence suggests that they can maintain optimal RDI of standard chemotherapy regimens. This study investigated the RDI of newer adjuvant chemotherapy regimens in this demographic.

Patients and Methods

We retrospectively analysed 281 patients ≥65 years who were diagnosed with ESBC and received adjuvant chemotherapy across three sites in QLD, Australia during 2010-2015. The primary endpoint was the proportion of patients who received an RDI≥85%.

Results

The median age at diagnosis was 68 (65-85) years old, with 36.3% over 70 years of age. Patient characteristics included tumour stage T3 or T4 (17%) and node positive disease (60%). Common chemotherapy regimens included docetaxel/cyclophosphamide (TC) (23%), 5-fluorouracil/epirubicin/ cyclophosphamide-docetaxel or paclitaxel (FEC-D/T) (17%), adriamycin/cyclophosphamide-weekly paclitaxel (AC-wT) (38%) and docetaxel/carboplatin/Herceptin (TCH) (11%). Primary (15%) and secondary (54%) G-CSF was used. RDI≥85% was achieved in 63% of patients. Significant associations were noted between reduced RDI and age ≥70 years ($p<0.001$), Charlson index 1+($p=0.043$), initial dose reductions ($p=0.01$), secondary G-CSF use ($p=0.45$), hospital admission ($p<0.001$) and febrile neutropenia ($p=0.007$). Treatment-related toxicities were the most common reason for non-completion with high rates of hospital admissions (46%) and febrile neutropenia (22%).

Conclusion

Our findings suggest that patients ≥ 65 years old with ESBC can maintain an optimal RDI of modern chemotherapy regimens. Appropriate geriatric assessment and use of supportive measures such as G-CSF could better assist select groups to maintain optimal dose intensity.

Introduction

Breast cancer is the leading cause of cancer and the second leading cause of cancer-related deaths among Australian women. Its incidence increases with age, with 59% of new diagnoses occurring in patients aged 65 years or older and a median age of presentation of 61 years of age.[1] While the prognosis of primary breast cancer has improved significantly in recent decades, this trend is heavily skewed towards younger patients. According to the breast cancer mortality database compiled by the World Health Organization, women aged between 50 and 69 years and those aged 70 years and above have experienced median improvements in mortality during 1989 and 2006 of 21% and 2%, respectively.[2] Recent publications have noted that a potential major reason for this comparatively poor prognosis among the elderly cohort is under-utilization of adjuvant chemotherapy in this patient group.[3, 4] Older patients have been more likely to receive dose reductions and delays, thus reducing the overall relative dose intensity (RDI) of their treatment.[5]

Dose intensity refers to the measure of chemotherapy drug delivered per unit time (mg/m^2/week) and RDI is defined as the received dose intensity relative to the reference dose intensity. RDI is an important prognostic factor which reflects the degree of adherence to recommended chemotherapy regimens and, by extension, the safety and tolerability of these treatments. Importantly, the maintenance of RDI above a minimum optimal threshold of 85% has been shown to correlate with increased rates of disease-free survival and overall survival.[6-8] Literature suggests that a key cause of this age-based discrepancy in treatment was the historical consensus that adjuvant chemotherapy treatments are poorly tolerated by older patients, compared to their younger counterparts. Several older studies reported significantly higher rates of toxicities and mortality associated with first- and second-generation adjuvant regimens among elderly breast cancer patients, leading to caution when prescribing chemotherapy in this demographic. [5, 8-10] However, a growing body of evidence suggests that select older patients tolerate a range of adjuvant chemotherapy regimens better than previously thought and that they are capable of maintaining optimal dose intensity.[11-14]

The primary aim of this study is to assess whether patients 65 years of age and older who received adjuvant chemotherapy for early stage breast cancer maintained an RDI of 85% and over.

Materials and Methods

Subjects and Data Collection

A retrospective analysis was conducted of all patients aged 65 years or older who underwent surgical resection for early stage breast cancer and received adjuvant chemotherapy across three sites in QLD, Australia between 2010 and 2015. Patients receiving palliative intent treatment were excluded from the study. The primary outcome measure of this study was to assess the proportion of patients reaching a relative dose intensity of 85% and over. Secondary outcome measures were to assess factors affecting dose intensity including age, body mass index (BMI), Charlson Comorbidity Index, chemotherapy protocol and use of Granulocyte Colony Stimulating Factor (G-CSF) as well as toxicity data. RDI was analysed against disease recurrence and patient mortality. Low risk ethical approval HREC/15/QRBW/320 was granted for the study by the human research ethics committee with the need for individual patient consent waivered.

Dose Intensity

RDI was calculated as a ratio of actual dose intensity (ADI) to standard dose intensity (SDI). In order to calculate SDI (mg/m^2/week), the total chemotherapy dose standard to each protocol was divided by the standard duration of that protocol, including all planned cycles. To calculate ADI, the total chemotherapy dose received by each patient during their treatment was divided by the duration for which each patient received that chemotherapy protocol. If a patient received less than the planned number of cycles, then a dose of 0 was assigned to each missed cycle. The duration of treatment was calculated as the sum of the time taken for each cycle received and the standard time required for any missed cycles. Trastuzumab was not included in calculations and dose intensity was only recorded for the first chemotherapy regimen prescribed, until its completion or discontinuation.

Statistical Analysis

Patient characteristics, clinical and pathological factors were summarised using frequencies and percent for categorical variables and median (interquartile range (IQR)) for continuous variables. BMI categories were collapsed into <25 kg/m^2 and $\geq$ 25 kg/m^2 for logistic regression analyses. Associations between RDI and factors of interest were examined using a chi-square test or Fisher's exact test where appropriate. Association between RDI and age group was further examined using univariable and

multivariable logistic regression analyses. SPSS was used to analyse the data. The level of statistical significance was set at 0.05.

Results

Patient Characteristics

A retrospective review yielded 281 eligible patients whose clinical and pathological characteristics are listed in Table 1. The median age at diagnosis was 68 (65-85) years old with 102 patients (36%) aged 70 and above. Most patients presented with hormone receptor positive (77%), HER2 negative (77%), early T stage 1/2 (83%), node positive (60%), invasive ductal carcinoma (75%) and underwent mastectomy (64%) followed by post-operative radiotherapy (67%). Commonly used adjuvant chemotherapy regimens included adriamycin/cyclophosphamide-weekly paclitaxel (AC-wT), docetaxel/ cyclophosphamide (TC), 5-fluorouracil/ epirubicin/ cyclophosphamide-docetaxel (FEC-D), 5-fluorouracil/ epirubicin/ cyclophosphamide-paclitaxel (FEC-T), FEC 100, docetaxel/ doxorubicin/ cyclophosphamide (TAC), docetaxel/ carboplatin/ Herceptin (TCH), and weekly paclitaxel.

Compared to their older counterparts, patients aged 65-69 years had significantly higher rates of T1/2 disease (67%, compared to 33% of older patients aged ≥70 years), higher rates of HER 2 negativity (68%, compared to 32% of older patients) and higher rates of wide local excision (78%, compared to 22% of older patients). Older patients received equivalent rates of AC-wT (48% aged ≥70 years, compared to 52% of patients aged 65 to 69 years) but significantly higher rates of weekly paclitaxel (75%, compared to 25% of younger patients) and significantly lower rates of TC (20%, compared to 80% of younger patients), TAC (12%, compared to 88% of younger patients) and FEC-D/T (29%, compared to 71% of younger patients). There was no significant difference between other parameters including Charlson comorbidity index, ECOG performance status, TNM stage, hormone receptor status, number of admissions, rates of febrile neutropenia or use of G-CSF.

Tolerability and Feasibility of Chemotherapy

A total of 177 (63%) patients achieved an RDI ≥85%, with 121 (43%) maintaining an RDI of 100%. An RDI of <65 occurred in 49 (17%) of patients. Initial dose reduction or capping of the dose occurred in 29 (10%) of patients. Dose reductions occurred in 64 patients (23%), dose delays in 58 (21%) and dose delays over 2 weeks in 17 (6%) of patients. A total of 178 (63%) of patients completed all prescribed chemotherapy cycles, with the most common reasons for non-completion being treatment-related toxicities including febrile neutropenia in 62 (22%) and peripheral neuropathy in 145 (52%). Primary G-

CSF was used in 41 (15%) patients with the requirement of secondary G-CSF in 148 (54%) of patients. A high rate of primary G-CSF prophylaxis was used in TAC (75%) and FEC-D (58%) chemotherapy regimens. Febrile neutropenia occurred most often in TC (34%) followed by TCH (30%) chemotherapy protocols in those patients where primary prophylaxis was not given (table 2). A total of 129 (46%) of patients experienced one or more admissions with 49 (17%) experiencing two or more admissions. Treatment related toxicities and the use of G-CSF was not significantly different amongst patients aged 65-69 compared to those aged 70 and over.

Factors Associated with Relative Dose Intensity

There was a significant association between reduced RDI and age group >70 ($p<0.001$), Charlson index of 1+ ($p=0.043$), initial dose reduction ($p=0.001$), admission to hospital ($p<0.001$), rate of febrile neutropenia ($p=0.007$) and requirement for secondary G-CSF use ($p=0.045$). No significant association was noted between RDI and primary G-CSF use, BMI or individual chemotherapy protocol (table 3).

The results of univariable and multivariable logistic regression analyses of the relationship between RDI and age group and Charlson index are shown in table 4. Univariable analyses demonstrate that Charlson index and age were significantly associated with RDI ($p = 0.044$ and $p<0.001$, respectively). The odds of achieving optimum dose intensity was 75% lower (OR: 0.25, 95% CI: 0.15-0.41) in patients aged ≥70 years compared to the younger age group and 33% lower (OR: 0.67, 95%CI: 0.46-0.97) in patients with higher Charlson index (> 1) compared to those with a Charlson index of 0. The effect of age group was further examined by adjusting for Charlson index respectively in multivariable analyses. The effect of age group remained statistically significant with no considerable changes in odds ratios.

Clinical Outcomes

The median length of follow up was 43 (6-117) months. There was no statistically significant association between RDI and recurrence or overall mortality with 37 events of breast cancer recurrence and 32 deaths (see table 5).

Discussion

Maintenance of RDI

The results of this study demonstrate that a significant proportion of selected older patients with early stage breast cancer are capable of maintaining an optimal dose intensity of adjuvant chemotherapy. An RDI of 85% or greater was achieved by 63% of the cohort, with 43% of patients maintaining an RDI of

100%. We have compared these findings to those of several recent studies (table 6). In their retrospective review, Raza *et al.* (2009) found that a comparable 65% of patients aged 65 years and over maintained an RDI of ≥85% while receiving adjuvant chemotherapy.[12] However, studies by Nghamphaiboon *et al.* (2011), Oladipo *et al.* (2012) and Lyman *et al.* (2013) showed higher rates of optimal RDI among elderly patients: 75%, 78% and 81%, respectively.[11, 13, 15] There are several key methodological discrepancies that may account for these differences in outcomes. A large proportion of our cohort was treated with third-generation anthracycline- and taxane-based chemotherapy regimens such as FEC-D, FEC-T and TAC, whereas the other studies relied largely on first- and second-generation treatments. The only other use of newer protocols was by Raza *et al.* (2009) and Oladipo *et al.* (2012) in which 22% and 2% of patients, respectively, received FEC-D.[12, 13]

Another key difference is that several of these studies used considerably higher rates of primary prophylactic G-CSF in order to minimize rates of treatment-related febrile neutropenia and thus improve dose intensity. Although the present study failed to find an association between primary G-CSF use and RDI, it is important to note that the rate of primary G-CSF use among our cohort was too low to make firm conclusions. However, the use of secondary G-CSF did statistically improve the dose intensity. In the patient cohorts investigated by Nghamphaiboon *et al.* (2012) and Lyman *et al.* (2013), 100% and 81 % of patients received primary G-CSF prophylaxis, respectively, whereas only 15% of our patients received this treatment.[11, 15] This approach is widely supported in recent literature and current European and American consensus panels recommend consideration of G-CSF use in patients undergoing intermediate- or high-risk regimens who are at additional risk of developing febrile neutropenia, including those aged 65 years or above. [3, 4, 16, 17] However, under the Australian Pharmaceutical Benefits Scheme, G-CSF use in the adjuvant chemotherapy setting is limited. Growth factor support is only licenced for primary prophylaxis in initial cycles of certain regimens (such as TAC, which is infrequently used in the elderly population at present) and in other regimens only as secondary prophylaxis of febrile neutropenia or prolonged severe neutropenia.[18] This relative lack of local supportive care limits the applicability of international clinical trial data in Australia. Finally, as neither Raza *et al.* (2009) nor Nghamphaiboon *et al.* (2012) were primarily investigating elderly patients, who only comprised 22% (n=37) and 14% (n=24) of participants, respectively, the statistical power of their conclusions regarding patients aged 65 and over is limited compared to this large retrospective cohort.[12, 15]

Factors affecting RDI

Our results implicate age as an independent risk factor for reduced dose intensity; patients aged 70 years and over were significantly less likely to maintain an optimal dose intensity than those who were 65 to 69 years old. When attempting to correlate our findings with other literature, it was noted that there is a lack of research involving elderly cancer patients, especially those over 70 years of age (with some studies actively excluding this age bracket) and that the studies that do exist have yielded mixed results.[13, 19] Lyman *et al*. (2013) found that increasing age was not associated with risk for a sub-optimal RDI and although Oladipo *et al.* (2012) noted that fewer patients aged 70 years maintained an RDI ≥85% this figure fell short of statistical significance.[11, 13] By contrast, Shayne *et al*. (2007) investigated dose intensity in cancer patients aged 70 years and above and found that increasing age was associated with lower RDI ($p = 0.03$), most markedly in the age bracket of 80 years and above. As their cohort comprised 976 patients, the statistical power of these results is greater than that of the previously mentioned studies, however their results are not directly comparable to ours as only 13% of the patients had breast cancer and only 52% were treated with curative intent.[20] Other studies have implicated age ≥70 as a significant predictor of reduced RDI of chemotherapy, but none with a specific focus on early stage breast cancer.[21, 22] In our study, there was significant variation in the chemotherapy protocols prescribed to these two age groups. Older patients received lower rates of TC, FEC-D and TAC chemotherapy regimens and higher rates of weekly paclitaxel alone deemed more tolerable. Older patients with Her2 positive breast cancer might have continued on an anti-Her2 agent upon ceasing chemotherapy as an alternative, more tolerable treatment option.

Interestingly, Charlson Comorbidity Index scores were comparable between both age groups, which contradicts the higher rates of comorbidity reported among elderly patients in the literature.[23] This might simply reflect a selection bias of patients being seen in the medical oncology department for consideration of adjuvant therapies where patients with comorbidities are less likely to be referred and ultimately treated. Charlson Index was shown to have a significant impact on RDI maintenance, albeit to a lesser degree than age, which is in keeping with past research into this patient demographic.[24] One potential cause for this trend is the fact that co-existing major illness is known to adversely affect adherence to institutional therapeutic guidelines.[4, 25] However, as stated previously, the differences that we found in chemotherapy regimen prescription between age groups was not accounted for by co-morbidity status.

Obesity is another patient-related factor that has been independently implicated in causing reductions of RDI; however, this finding was not replicated among our cohort.[26, 27] While a higher proportion of patients with a BMI >24.9 failed to reach optimal DI, this assocation remained statistically insignificant.

Although there was a significant difference in choice of chemotherapy and maintaining RDI, there is likely to be a selection bias particularly related to comorbidities and performance status. For example, clinicians are more inclined to choose chemotherapy for Her2 positive early breast cancer, so that the patients can receive concurrent trastuzumab. Therefore, patients may be included for chemotherapy who otherwise would have received endocrine treatment without chemotherapy. This may explain the reduced RDI <85% with TCH (53%) and weekly paclitaxel (67%). In general terms, it has been shown that relative to first-generation adjuvant therapies, second-generation regimens are more efficacious in the treatment of early breast cancer and, importantly, are well tolerated in older patients.[28] While there is a comparative lack research into the tolerability of third-generation adjuvant cytotoxic regimens in this demographic, there is some evidence to suggests that newer, dose-intense anthracycline-based regimens are equally as effective across age groups, that they are significantly more effective than first generation regimens, and that they are tolerated in healthy elderly patients in the setting of primary G-CSF prophylaxis.[5, 10] Raza *et al.* (2009) recorded higher rates of optimal RDI with AC-wT, FEC-D and FEC-100 (96%, 95% and 71%, respectively), however, statistical power was also a limiting factor in this study.[12]

As expected, hospital admission during treatment was associated with significant reductions in RDI. It is important to note that the majority of reductions in RDI occurred after the first cycle and are thus attributable to unplanned factors such as treatment-related toxicity. The most pronounced treatment-related toxicity experienced by our cohort was febrile neutropenia (22%). RDI significantly improved with secondary GCSF use. The use of primary GCSF prophylaxis could ameliorate the risk of febrile neutropenia in this population and further improve RDI.

Prognostic Significance of RDI

There were few recurrences or deaths to date amongst our cohort within the short follow up period. As such, we did not find a significant association between RDI and cancer recurrence, all-cause mortality or cancer-specific mortality. Although some studies fail to report worse outcomes associated with reductions in RDI, the weight of research supports the prognostic significance of dose intensity.[6, 7, 29, 30]

Early breast cancer survival rates associated with DI < 65% are comparable to those of untreated control groups and a dose reduction of 20% has been show to halve rates of cure in this demographic.[31]

Study Limitations

This study has a number of limitations, chief among them being the relatively small sample size of this which resulted in insufficient statistical power to analyse the effect of chemotherapy regimen on RDI. In addition, the brief follow-up period did not allow for conclusive assessment of the prognostic significance of RDI. Other sources of inaccuracy are the broad manner in which toxicity data is recorded as per the CTCAE 1.1 reference and the difficulty in accessing records of non-Queensland Health hospital admissions. Finally, selection bias must also be taken into account: poor health and performance status likely prevented many older; less fit patients from being referred for consideration of adjuvant chemotherapy and, in the event of successful referral, these patients may have been less likely to receive treatment than their younger counterparts. As such feasibility and tolerability and data is likely skewed by the resulting younger, healthier cohort. However, this is conjecture as total numbers of patients considered for referral and for treatment were not recorded.

Conclusion

Our results show that patients ≥65 years with early stage breast cancer can maintain an optimal RDI through a range of newer adjuvant chemotherapy protocols; however, tolerance of these regimens remains suboptimal, with high rates of treatment-related toxicities necessitating admission and treatment delay. Given its prognostic importance, it is essential to minimize reductions in RDI through the early and widespread use of supportive measures including secondary G-CSF prophylaxis, particularly in at risk populations identified in this study, as well as through the effective management of treatment-related toxicities. The routine use of comprehensive geriatric assessment in older patients may have a role to play in the latter, although more research is required in this area.[32] There continues to be a paucity of clinical research in elderly cancer patients necessitating larger scale investigation into factors influencing RDI in this demographic, especially with regards to newer chemotherapy regimens.

Disclosures

Rahul Ladwa has received funding for travel and accommodation by MSD.

Natasha Woodward has received funding for travel and accommodation by Roche as well as researching funding by Medivation and travel support from CSL. Natasha also holds stock/interest in CSL.

David Wyld has received travel support for conferences, been a paid speaker, attended advisory boards, and received research funding in terms of unrestricted educational grants to his institution from Novartis and Ipsen Australia.

The other authors have no declarations of interest.

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Table 1. Patient Demographics and Treatments Used

Variables	N (%)	Variables	N (%)
Gender		Hormone Receptor Status	
Female	279 (99)	Positive	217 (77)
Male	2 (1)	Negative	64 (23)
BMI category		HER2 status	
<25 kg/m^2	84 (30)	Positive	65 (23)
≥ 25 kg/m^2	197 (70)	Negative	216 (77)
Charlson index		Surgery	
< 1	178 (63)	Wide Local Excision	102 (36)
1 or above	103 (37)	Mastectomy	179 (64)
ECOG performance status		Adjuvant External Radiation therapy	
< 1	243 (87)	Yes	188 (67)
1 or above	38 (13)	No	93 (33)
Tumour stage		Neoadjuvant therapy	
1/2	234 (83)	Yes	21 (8)
3/4	47 (17)	No	260 (92)
Simplified tumour type		Chemotherapy Protocols Used	
IDC	210 (75)	AC-wT	106 (38)
ILC	44 (16)	TC	64 (23)
Other	27 (9)	FEC-D/ FEC-T	48 (17)
		TAC	8 (3)
Positive lymph nodes		TCH	30 (11)
< 1	111 (40)	Paclitaxel	12 (4)
1 or above	170 (60)	FEC 100	8 (3)
		Other	5 (1)

Body Mass Index (BMI), Eastern Cooperative Oncology Group (ECOG), invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC), human epidermal growth factor receptor 2 (HER 2), adriamycin/cyclophosphamide-weekly paclitaxel (AC-wT), docetaxel/ cyclophosphamide (TC), 5-fluorouracil/ epirubicin/ cyclophosphamide-docetaxel (FEC-D), 5-fluorouracil/ epirubicin/ cyclophosphamide-paclitaxel (FEC-T), docetaxel/ doxorubicin/ cyclophosphamide (TAC), docetaxel/ carboplatin/ Herceptin (TCH).

Table 2. Association of G-CSF Use and Rate of Febrile Neutropenia with Chemotherapy Protocol Used.

				Chemotherapy protocol											
				AC-wT		TC		Paclitaxel		TCH		FEC-D		TAC	
				N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Primary G-CSF	Y			2	2%	5	8%	0	0%	0	0%	28	58%	6	75%
	N			104	98%	59	92%	12	100%	30	100%	20	42%	2	25%
		FN	Y	15	14%	20	34%	0	0%	10	33%	6	30%	1	50%
			N	89	86%	39	66%	12	100%	20	67%	14	70%	1	50%
Secondary G-CSF	Y			73	71%	38	61%	0	0%	18	60%	8	17%	2	25%
	N			30	29%	24	39%	11	100%	12	40%	40	83%	6	75%

Granulocyte Colony Stimulating Factory (G-CSF), Febrile Neutropenia (FN), adriamycin/cyclophosphamide-weekly paclitaxel (AC-wT), docetaxel/ cyclophosphamide (TC), 5-fluorouracil/ epirubicin/ cyclophosphamide-docetaxel (FEC-D), docetaxel/ doxorubicin/ cyclophosphamide (TAC), docetaxel/ carboplatin/ Herceptin (TCH).

Table 3. Associations Between Relative Dose Intensity (RDI) and Clinical-Pathological Factors

Variable	RDI <85%: N (%)	RDI ≥85 %: N (%)	p-value
Age group			<0.001
65 to 69	45 (25)	134 (75)	
70 and above	59 (58)	43 (42)	
BMI			0.27
18.5 to 24.9	27 (32)	57 (68)	
25 and above	77 (39)	120 (61)	
Charlson Index			0.043
< 1	58 (33)	120 (67)	
1 or above	46 (45)	57 (55)	
Initial dosage			0.001
<100%	19 (65)	10 (35)	
100%	85 (34)	167 (66)	
Admissions			<0.001
Yes	68 (54)	58 (46)	
No	36 (23)	119 (77)	
Febrile neutropenia			0.007
Yes	32 (52)	30 (48)	
No	72 (33)	147 (67)	
Primary G-CSF			0.447
Yes	13 (32)	28 (68)	
No	91 (38)	149 (62)	
Secondary G-CSF			0.045
Yes	45 (30)	103 (70)	
No	53 (42)	73 (58)	
Peripheral Neuropathy			0.564
Yes	56 (39)	89 (61)	
No	48 (35)	88 (65)	
Chemotherapy Protocol			0.029
AC-T	40 (38)	66 (62)	
TC	16 (25)	48 (75)	
FEC-D/FEC-T	18 (37)	30 (63)	
TAC	1 (13)	7 (88)	
TCH	16 (53)	14 (47)	
Paclitaxel	8 (67)	4 (33)	
Other (FEC-100, AC)	5 (38)	8 (62)	

Body Mass Index (BMI), Granulocyte Colony Stimulating Factory (G-CSF), adriamycin/cyclophosphamide-weekly paclitaxel (AC-wT), docetaxel/ cyclophosphamide (TC), 5-fluorouracil/ epirubicin/ cyclophosphamide-docetaxel (FEC-D), 5-fluorouracil/ epirubicin/ cyclophosphamide-paclitaxel (FEC-T), docetaxel/ doxorubicin/ cyclophosphamide (TAC), docetaxel/ carboplatin/ Herceptin (TCH).

Table 4. Logistic Regression Analyses of Factors Affecting Relative Dose Intensity (RDI)

	Univariable		**Multivariable** Age and Charlson index	
Variable	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age group		<0.001		< 0.001
65 to 69	1.00		1.00	
70 and above	0.25 (0.15-0.41)		0.24 (0.14-0.41)	
Charlson index		0.034		0.038
< 1	1.00		1.00	
1 or above	0.67 (0.46-0.97)		0.57 (0.34-0.97)	

Table 5. Associations Between Relative Dose Intensity (RDI) and Outcomes of Chemotherapy

Variable	RDI <85%: n (%)	RDI ≥ 85%: n (%)	p-value
Recurrence			0.399
Yes	16 (15)	21 (12)	
No	88 (85)	156 (88)	
All-Cause Mortality			0.951
Yes	12 (12)	20 (11)	
No	92 (88)	157 (89)	

Table 6. Retrospective Studies of Relative Dose Intensity (RDI) of Adjuvant Chemotherapy in Older Patients with Breast Cancer

	Med Onc 2009 (13) N = 37	Med Onc 2012 (15) N=24	Breast J 2012 (14) N= 101	Br Ca R+T 2013 (12) N = 117	Current study N = 281
Median Age	n/a	72	69	n/a	68
Chemo Protocol					
CMF	-	-	8	-	-
FEC-100	22	-	77	-	8
AC	-	-	14	9	-
AC-T	7	-	-	18	106
TC	-	24	-	61	64
TCH	-	-	-	15	30
FEC-D/T	8	-	2	-	48
TAC	-	-	-	-	8
Paclitaxel	-	-	-	-	12
RDI ≥85%	65%	75%	78%	81%	63%
Dose delay > 7 days	10.8%	8%	44%	24%	21%
Primary G-CSF prophylaxis	0	100%	n/a	81%	15%

Granulocyte Colony Stimulating Factory (G-CSF), adriamycin/cyclophosphamide-weekly paclitaxel (AC-wT), docetaxel/ cyclophosphamide (TC), 5-fluorouracil/ epirubicin/ cyclophosphamide-docetaxel (FEC-D), 5-fluorouracil/ epirubicin/ cyclophosphamide-paclitaxel (FEC-T), docetaxel/ doxorubicin/ cyclophosphamide (TAC), docetaxel/ carboplatin/ Herceptin (TCH).