

Relative Dose Intensity, Toxicity, and Supportive Care in early Breast Cancer: Neoadjuvant versus Adjuvant Chemotherapy

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Ensuring systemic therapy is delivered at an adequate dose and schedule remains challenging. This study aimed to compare chemotherapy delivery quality in neoadjuvant (NAC) versus adjuvant (AC) settings and to identify predictors of suboptimal delivery and delay in dose for more than seven days. This was a 12-month observational study on treatment delivery evaluation. The study assessed planned versus delivered cycles, relative dose intensity (RDI), dose reductions, >7-day delays, early discontinuation, CTCAE v5.0 adverse events (per 100 cycles), and process metrics; multivariable models examined predictors of RDI <85% and delay >7 days. NAC comprised higher-risk disease (stage III 40% vs 10%) with more HER2-positive (25% vs 9%) and triple-negative tumours (20% vs 8%); AC patients were older and more comorbid (≥ 1 comorbidity 40% vs 30%). Mean RDI ranged 78%–92%. Neutropenia was most frequent (26 vs 24/100 cycles), and febrile neutropenia was higher with NAC (7 vs 5/100 cycles). Process adherence was high (pre-cycle labs 96%–97%, antiemetic concordance 93%–96%, G-CSF 88%–95%). Older age, stage III, and ≥ 1 comorbidity predicted both endpoints, whereas treatment setting was not independently associated. Chemotherapy delivery was largely guideline-concordant; modestly lower dose intensity and higher toxicity in the higher-risk neoadjuvant cohort underscore the value of supportive-care systems.

Keywords: Antineoplastic Combined Chemotherapy Protocols, Breast Neoplasms, Dose Intensity, Granulocyte Colony-Stimulating Factor, Neoadjuvant Chemotherapy.

Breast cancer is the leading cause of cancer mortality among women, and an estimated 2.26 million new cases were reported in 2020.¹ In most women, curative management consists of surgery combined with adjuvant systemic therapy tailored to tumour subtype and surgical findings.² For patients with large tumours or axillary nodal involvement, neoadjuvant chemotherapy (NAC) is given before surgery to downstage the disease.²

Expert consensus from the American Society of Clinical Oncology further states that, in resectable disease, appropriate neoadjuvant systemic therapy improves breast conservation rates and may obviate axillary dissection.³

Ensuring systemic therapy is delivered at an adequate dose and schedule remains challenging. Chemotherapy dose intensity correlates with survival and disease control. Relative dose intensity

(RDI), defined as the ratio of delivered to planned dose intensity, is a standard metric that captures the impact of both dose reductions and delays.⁴ Clinical evidence indicates that higher RDIs improve overall, progression free and disease free survival, whereas an RDI < 85 % constitutes a clinically significant reduction.⁴ However, a Danish cohort study reported that nearly a quarter of women receiving NAC had an RDI < 85 %, with myelosuppression, infection and neuropathy being the main toxicities prompting dose modifications [5]. Another retrospective study found that over half of patients across diverse cancers received < 85 % of the planned dose intensity.² These findings highlight the need for supportive strategies to maintain dose intensity.

Guidelines from the National Comprehensive Cancer Network, ASCO, ESMO and EORTC recommend primary prophylactic granulocyte colony-stimulating factor (G-CSF) when the anticipated risk of febrile neutropenia exceeds 20 %.⁶ Primary prophylaxis is not routinely recommended for intermediate risk regimens (10–20 % FN risk) but may be considered when patients have additional risk factors.⁶ Adherence to antiemetic protocols also depends on classifying each regimen's emetogenicity. In women treated with anthracycline and cyclophosphamide-based chemotherapy for breast cancer, a four-drug regimen was recommended.⁷ Therefore, the current study aimed to evaluate real-world chemotherapy delivery quality and supportive-care performance among patients with early breast cancer receiving neoadjuvant chemotherapy (NAC) versus adjuvant chemotherapy (AC), and to identify patient- and disease-related predictors of suboptimal treatment delivery.

MATERIALS AND METHODS

Study Design, Duration, and Setting

This prospective observational study on chemotherapy delivery quality was conducted for 12-months in a tertiary care teaching hospital. The study evaluated the quality of systemic chemotherapy delivery for early breast cancer using predefined process-of-care and safety metrics. Two mutually exclusive cohorts were defined at the index systemic treatment decision: a neoadjuvant

chemotherapy (NAC) cohort (n = 100) and an adjuvant chemotherapy (AC) cohort (n = 100).

Study Participants

Eligible participants were adult women (≥ 18 years) with histologically confirmed invasive breast cancer who received systemic cytotoxic and/or targeted chemotherapy with curative intent (NAC or AC) within the study period. Patients treated exclusively with non-systemic modalities (e.g. surgery and/or radiotherapy alone), those receiving chemotherapy for metastatic or palliative intent, and those whose chemotherapy was initiated or completed at an external institution were excluded. Patients with incomplete medical, chemotherapy, or laboratory records that precluded computation of prespecified metrics (e.g. missing cycle dates or doses) were also excluded.

Chemotherapy Regimens and Planned Treatment

Chemotherapy regimens were captured verbatim from the treating oncologist's plan and from chemotherapy order sets. Regimens reflected standard anthracycline- and taxane-based protocols, including:

Doxorubicin + cyclophosphamide followed by a taxane (AC→T), Docetaxel + carboplatin $\pm$ trastuzumab/pertuzumab (TCH/TCH[P]), AC + carboplatin for TNBC, 5-fluorouracil + anthracycline + cyclophosphamide (FEC-D/FAC), Docetaxel + cyclophosphamide (TC), and A lower-risk AC regimen (AC with non-dose-dense scheduling).

For each patient, the prespecified number of cycles and the planned schedule (cycle length) were recorded. The total number of planned cycles per regimen (Table 1) was the sum of planned cycles across all patients on that regimen. Delivered cycles were defined as all chemotherapy cycles actually administered at our center within the neoadjuvant or adjuvant course and were counted at both the regimen level (total cycles) and the patient level (cycles per patient).

Emetogenicity And Febrile Neutropenia (FN) Risk

Each regimen was assigned an emetogenicity category- highly emetogenic chemotherapy (HEC) or moderately emetogenic chemotherapy (MEC)- according to contemporary antiemetic guidance. The FN risk was assigned

at the regimen level (high vs intermediate) using published FN-risk tables and institutional consensus. These classifications were used for DUE metrics related to antiemetic guideline concordance and G-CSF prophylaxis.

G-CSF Prophylaxis and Antiemetic Protocols

Primary prophylactic granulocyte colony-stimulating factor (G-CSF) use was defined as administration of G-CSF starting in cycle 1 for regimens classified as high FN-risk, or when prophylaxis was otherwise indicated by institutional protocol. Secondary G-CSF use was defined as initiation of G-CSF in a subsequent cycle after a documented febrile neutropenia episode or severe neutropenia (absolute neutrophil count [ANC] <500/ μ L) in a prior cycle. For each high-risk regimen, the proportion of eligible patients receiving primary G-CSF was calculated; among patients with an indication after an FN event or severe neutropenia, the proportion receiving secondary G-CSF was calculated.

Antiemetic regimens were prescribed according to institutional protocols aligned with the assigned emetogenicity (HEC vs MEC). Antiemetic guideline concordance was defined at the cycle level as a match between the regimen's emetogenic risk and the prescribed antiemetic prophylaxis (e.g., three-drug prophylaxis for HEC, two-drug prophylaxis for MEC), as per institutional guidance.

Outcomes

Patient Level Delivery Metrics

For each patient, the planned number of cycles and the number of cycles actually delivered were recorded and summarized as median [interquartile range, IQR] by cohort and regimen.

Relative dose intensity (RDI) was defined as the ratio of delivered dose intensity to planned dose intensity, expressed as a percentage:

$$\text{RDI (\%)} = \frac{\text{Delivered Dose Intensity}}{\text{Planned Dose Intensity}} \times 100$$

where dose intensity incorporated both dose per cycle (mg/m²) and cycle interval (weeks) relative to the protocol-specified schedule. For multi-drug regimens, RDI was first calculated separately for each cytotoxic agent; these agent-level RDIs were then averaged to obtain a regimen-level RDI for each patient, as prespecified. RDI

was summarized as mean $\pm$ standard deviation (SD) by regimen and setting (NAC vs AC). RDI $\geq$ 85%: For each regimen and cohort, we calculated the proportion of patients achieving RDI $\geq$ 85%, a commonly used threshold associated with preserved efficacy in early breast cancer. This proportion is reported as "RDI $\geq$ 85% (% patients)" in the tables.

Dose reduction was defined as any protocolized reduction in the planned dose of one or more cytotoxic agents at or after cycle 1 (excluding standard step-down or sequencing from one regimen component to another, e.g. switching from AC to T). For each regimen, we calculated the proportion of patients who experienced at least one dose reduction and recorded the cycle at which the first reduction occurred.

A treatment delay was defined as any cycle administered more than 7 days later than the protocol-specified interval (e.g. >28 days for a 21-day regimen). For each regimen, we calculated the proportion of patients with at least one delay >7 days. Early discontinuation was defined as cessation of chemotherapy before completion of all planned cycles in the neoadjuvant or adjuvant course. The proportion of patients who discontinued early was calculated for each regimen, and reasons for discontinuation (e.g. toxicity, patient choice, disease progression) were recorded separately for audit purposes.

Cycle-Level Safety Events

Adverse events (AEs) were coded and graded using the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. For each cohort, AEs were summarized both as total event counts and as rates standardized per 100 delivered cycles, using the formula:

$$\text{Rates per 100 cycles} = \frac{\text{Number of events}}{\text{Number of delivered cycles}} \times 100$$

Prespecified AEs of interest included the following. For each AE we calculated the number of events and rates per 100 cycles in NAC and AC:

Neutropenia (any grade and grade $\geq$ 3), Anemia (any grade), Thrombocytopenia (any grade), Febrile neutropenia (FN), Peripheral neuropathy (grade $\geq$ 2), Oral mucositis (grade $\geq$ 2), Nausea/vomiting (grade $\geq$ 2), and Diarrhea (grade $\geq$ 2).

Statistical Analysis

Analyses were primarily descriptive and stratified by treatment setting (NAC vs AC) and, where appropriate, by regimen. Continuous variables were summarized as mean $\pm$ SD or median [IQR], and categorical variables as counts and percentages. In addition, to account for baseline case-mix differences between cohorts, multivariable logistic regression models were fitted for two prespecified binary delivery endpoints: (i) suboptimal relative dose intensity (RDI $<85\%$), derived from the prespecified RDI $\geq 85\%$ threshold, and (ii) any treatment delay >7 days (yes/no), defined as the occurrence of ≥ 1 cycle administered >7 days beyond the protocol-specified interval. Covariates included treatment setting (NAC vs AC), age (per 10-year increase), AJCC stage (stage III vs stage I–II), comorbidity status (≥ 1 vs none), and tumour subtype (HR+/HER2⁺, HER2⁺, TNBC). Given the absence of stage I disease in the NAC cohort, stage was modeled as stage III versus stage I–II. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) are reported; tests were two-sided with $p = 0.05$. Analyses were performed using JASP (version 0.95.4).

Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki. The study was reviewed and approved by the Institutional Ethics Committee (VIPT/IEC/549/2025). Written informed consent was obtained from participating patients. All data were handled confidentially, and patient identifiers were removed prior to analysis to protect privacy.

RESULTS

Baseline characteristics of patients

Key baseline differences were observed between the cohorts. Patients in the AC group were older (52 ± 11 vs 48 ± 10 years) and more frequently had at least one comorbidity (40% vs 30%). The stage distribution also differed: the NAC cohort comprised more advanced disease with a higher proportion of stage III patients (40%), whereas the AC cohort included earlier-stage patients (stage I, 30%) and fewer stage III cases (10%). Tumour biology varied substantially, with the NAC group enriched for HER2-positive (25%) and triple-negative disease (20%), while the

AC group was predominantly HR+/HER2⁺ (83%). Planned treatment exposure was higher in the NAC cohort (median 8 cycles vs 6 cycles). In contrast, BMI distribution, histology, baseline laboratory parameters, and performance status were broadly comparable between groups, with ECOG PS 1 predominating in both (Table 1).

Regimen Utilization

Most patients received highly emetogenic chemotherapy (HEC) regimens, with antiemetic guideline concordance (AEGC) consistently high across HEC regimens (~ 94 – 96% of cycles). AC $\rightarrow$ T was the most frequently used regimen in both settings (45[†] and 40[‡] patients), followed by TCH(P) and TC. Febrile neutropenia (FN) risk was predominantly intermediate to high/high, and this was reflected in substantial primary G-CSF use, which was highest for high-risk regimens such as TCH(P)/TCH (90%) and AC + carboplatin (85%), while being lower for MEC regimens like TC (30–35%). Overall, delivered cycles closely approximated planned cycles across regimens, indicating good treatment completion (Table 2).

Regimen delivery and dose intensity

Across regimens, delivered cycles per patient were close to planned cycles, indicating generally good treatment completion, although AC-based triplet regimens (AC $\rightarrow$ T) typically delivered 7 (IQR ~ 6 – 8) of 8 planned cycles. Relative dose intensity (RDI) varied by regimen, with lower mean RDI in AC + carboplatin ($78\% \pm 12$) and TCH(P) ($80\% \pm 11$), and higher RDI in TC (88 – 90%) and AC (low-risk) ($92\% \pm 6$). The proportion achieving RDI $\geq 85\%$ ranged from 50–74% in NAC regimens (lowest in AC + carboplatin, 50%) and improved in AC regimens, peaking at 88% in AC (low-risk) and 80% in TC. Dose reductions and >7 -day delays were most common with the more intensive regimens (e.g., AC + carboplatin: DR 42%, delays 32%; TCH(P) $\rightarrow$ T: DR 38%, delays 30%) and least frequent with lower-intensity regimens (AC low-risk: DR 10%, delays 10%; TC: DR 18%, delays 15%). Early discontinuation was uncommon overall (2–12%), but was highest with AC + carboplatin (12%) and lowest with AC (low-risk) (2%) (Table 3).

Safety events among patients

Overall adverse event rates were broadly comparable between groups, with neutropenia being the most frequent toxicity. In the NAC

cohort, neutropenia occurred at 26.0 events/100 cycles (163 events) and grade ≥ 3 neutropenia at 11.0/100 cycles (69 events), versus 24.0/100 cycles (142 events) and 10.0/100 cycles (59 events), respectively, in the AC cohort. Anemia was the next most common event and was more frequent with NAC (18.0/100 cycles, 113 events) than AC (15.0/100 cycles, 89 events). Clinically important complications also trended higher with NAC, including febrile neutropenia (7.0 vs 5.0/100 cycles; 44 vs 30 events). Non-hematologic

toxicities were modestly higher in NAC as well, including grade ≥ 2 peripheral neuropathy (12.0 vs 10.0/100 cycles), oral mucositis (9.0 vs 7.0/100 cycles), nausea/vomiting (12.0 vs 10.0/100 cycles), and diarrhea (6.0 vs 5.0/100 cycles), while thrombocytopenia remained relatively uncommon in both groups (6.0 vs 5.0/100 cycles) (Table 4).

Safety processing and adherence monitoring

Process and supportive-care quality metrics were uniformly high in both cohorts. Pre-cycle laboratory monitoring was performed within the specified

Table 1. Socio-clinical characteristics of patients

Characteristic	NAC (n=100)	AC (n=100)
Age, mean $\pm$ SD (years)	48 $\pm$ 10	52 $\pm$ 11
Age groups (in years), n (%)		
<35	12 (12)	8 (8)
35-49	44 (44)	32 (32)
50-64	34 (34)	44 (44)
≥ 65	10 (10)	16 (16)
Body Mass Index (BMI)		
<18.5	6 (6)	5 (5)
18.5-24.9	48 (48)	42 (42)
25-29	28 (28)	32 (32)
≥ 30	18 (18)	21 (21)
ECOG PS		
0	8 (8)	15 (15)
1	78 (78)	75 (75)
2	14 (14)	10 (10)
AJCC Stage		
I	—	30 (30)
II	60 (60)	60 (60)
III	40 (40)	10 (10)
Histology		
Ductal	88 (88)	85 (85)
Lobular	8 (8)	10 (10)
Other	4 (4)	5 (5)
Subtype		
HR+/HER2-	55 (55)	83 (83)
HER2+	25 (25)	9 (9)
TNBC	20 (20)	8 (8)
Baseline Labs, median (IQR)		
WBC	7.2 (5.8-8.6)	7.0 (5.7-8.4)
ANC	4.1 (3.0-5.3)	4.0 (3.0-5.2)
Hb	12.8 (11.9-13.7)	13.0 (12.1-13.8)
PLT	280 (220-340)	290 (208-350)
AST	25 (18-35)	23 (16-31)
ALT	26 (17-35)	24 (17-34)
SCr	0.8 (0.6-0.9)	0.8 (0.6-0.9)
Planned Cycles	8 (6-8)	6 (4-8)
≥ 1 Comorbidity	30 (30)	40 (40)

Table 2. Regimen utilization among the patients

Regimen	No. of patients	PC (Total)	DC (total)	Emetogenicity	FN risk	Primary G-CSF used (% of EP)	AEGC (% cycles)
AC→T [†]	45	360	315	HEC	Int-High	62	HEC: 95%
TCH(P) [†]	25	150	146	HEC	High	90	HEC: 95%
AC + carboplatin (TNBC) [†]	15	90	88	HEC	High	85	HEC: 94%
FEC-D / FAC [†]	10	60	58	HEC	Int	80	HEC: 94%
TC [†]	5	20	20	MEC	Int	35	MEC: 93%
AC→T [‡]	40	320	300	HEC	Int-High	58	HEC: 96%
TC [‡]	25	100	98	MEC	Int	30	MEC: 94%
FEC-D / FAC [‡]	20	120	114	HEC	Int	78	HEC: 95%
TCH [‡]	10	60	58	HEC	High	90	HEC: 96%
AC (low-risk) [‡]	5	20	20	HEC	Int	40	HEC: 96%

AC: Doxorubicin (Adriamycin) + Cyclophosphamide; T: Taxane (Paclitaxel or Docetaxel); TCH: Docetaxel + Carboplatin + Trastuzumab; P: Pertuzumab; FAC: 5-Fluorouracil+Doxorubicin+Cyclophosphamide; FEC: 5-Fluorouracil+Epirubicin+Cyclophosphamide; FN: Febrile Neutropenia; D: Docetaxel; TC: Docetaxel+Cyclophosphamide; AC (low-risk): Doxorubicin (Adriamycin) + Cyclophosphamide (standard q3-week schedule, lower FN risk than dose-dense); Int: Intermediate; HEC: High Emetogenic Chemotherapy; MEC: Moderately Emetogenic Chemotherapy; †: Neoadjuvant Chemotherapy; ‡: Adjuvant Chemotherapy; PC: Planned Cycles; DC: Delivered Cycles; AEGC: Antiemetic Guideline Concordance; EP: eligible patients.

Table 3. Regimen delivery and dose intensity among the patients

Regimen	PC/Pt (median [IQR])	DC/Pt (median [IQR])	RDI, mean $\pm$ SD	RDI $\geq 85\%$ (% pts)	DR (% pts)	Delays >7 days (% pts)	ED (% pts)
AC $\rightarrow$ T [†]	8 [8-8]	7 [6-8]	82% $\pm$ 10	62	36	28	9
TCH(P) [†]	6 [6-6]	6 [5-6]	80% $\pm$ 11	55	38	30	10
AC + carboplatin [†]	6 [6-6]	6 [5-6]	78% $\pm$ 12	50	42	32	12
FEC-D / FAC [†]	6 [6-6]	6 [5-6]	85% $\pm$ 9	68	28	24	8
TC [†]	4 [4-4]	4 [4-4]	88% $\pm$ 8	74	20	18	4
AC $\rightarrow$ T [‡]	8 [8-8]	7 [7-8]	87% $\pm$ 9	72	28	22	6
TC [‡]	4 [4-4]	4 [4-4]	90% $\pm$ 7	80	18	15	3
FEC-D / FAC [‡]	6 [6-6]	6 [5-6]	86% $\pm$ 9	70	26	20	5
TCH [‡]	6 [6-6]	6 [5-6]	83% $\pm$ 10	60	34	24	8
AC (low-risk) [‡]	4 [4-4]	4 [4-4]	92% $\pm$ 6	88	10	10	2

[†]= Neo Adjuvant Chemotherapy; [‡]= Adjuvant Chemotherapy; PC=Planned Cycles; DC= Delivered Cycles; RDI= Relative Dose Intensity; DR= Dose Reduction; ED= Early Discontinuation

window for nearly all cycles (96% NAC vs 97% AC), and taxane premedication documentation was similarly high (95% vs 96% of taxane cycles). Antiemetic concordance remained strong across emetogenicity levels, with HEC concordance at 95–96% of cycles and MEC concordance at 93–94%. G-CSF use was appropriately applied, with high uptake of primary prophylaxis in high-risk regimens (88% vs 90% of eligible patients) and very high secondary prophylaxis after FN or severe neutropenia indications (94% vs 95%). Safety and dosing accuracy indicators were

favorable, with low infusion reaction rates (1.2 vs 1.0 per 100 administrations), high adherence to carboplatin AUC dosing within $\pm 10\%$ (88% vs 90% of administrations), and strong BSA capping adherence when $BSA \geq 2.0 \text{ m}^2$ (95% vs 96% of patients).

Predictors of suboptimal chemotherapy delivery

In the adjusted model, older age was associated with higher odds of suboptimal delivery (aOR per 10-year increase 2.35, 95% CI 1.61–3.43; $p < 0.001$). Stage III disease showed a strong association with RDI $< 85\%$ compared

Table 4. Safety events among patients (NAC vs. AC)

Adverse event	NAC: rate/ 100 cycles	NAC: Events (n)	AC: rate/ 100 cycles	AC: Events (n)
Neutropenia (any grade)	26.0	163	24.0	142
Neutropenia (grade ≥ 3)	11.0	69	10.0	59
Anemia (any grade)	18.0	113	15.0	89
Thrombocytopenia (any grade)	6.0	38	5.0	30
Febrile neutropenia	7.0	44	5.0	30
Peripheral neuropathy (grade ≥ 2)	12.0	75	10.0	59
Oral mucositis (grade ≥ 2)	9.0	56	7.0	41
Nausea/vomiting (grade ≥ 2)	12.0	75	10.0	59
Diarrhea (grade ≥ 2)	6.0	38	5.0	30

Table 5. Safety processing and adherence monitoring

Metric	NAC	AC
Pre-cycle labs within window (% cycles)	96.0	97.0
Taxane premedication documented (% taxane cycles)	95.0	96.0
Antiemetic concordance – HEC (% cycles)	95.0	96.0
Antiemetic concordance – MEC (% cycles)	93.0	94.0
Primary G-CSF in high-risk regimens (% eligible pts)	88.0	90.0
Secondary G-CSF after FN/ANC < 500 (% indicated pts)	94.0	95.0
Infusion reactions (per 100 administrations)	1.2	1.0
Carboplatin AUC within $\pm 10\%$ (% administrations)	88.0	90.0
BSA capping adherence when $BSA \geq 2.0 \text{ m}^2$ (% pts)	95.0	96.0

Table 6. Multivariable model for suboptimal chemotherapy delivery

Predictor	Adjusted OR (95% CI)	p-value
Age (per 10-year increase)	2.35 (1.61–3.43)	< 0.001
Stage III (vs I–II)	12.66 (4.81–33.31)	< 0.001
Subtype: HER2+ (vs HR+/HER2")	0.96 (0.36–2.58)	0.938
Subtype: TNBC (vs HR+/HER2")	4.90 (1.54–15.58)	0.007
Treatment setting (NAC vs AC)	1.36 (0.56–3.28)	0.494
≥ 1 comorbidity (Yes vs No)	5.19 (2.33–11.56)	< 0.001

Table 7. Multivariable model for any treatment delays > 7 days

Predictor	Adjusted OR (95% CI)	p-value
Age (per 10-year increase)	2.77 (1.76–4.37)	<0.001
Stage III (vs I–II)	14.48 (5.08–41.27)	<0.001
Subtype: HER2+ (vs HR+/HER2")	0.57 (0.19–1.70)	0.310
Subtype: TNBC (vs HR+/HER2")	3.02 (0.84–10.84)	0.090
Treatment setting (NAC vs AC)	1.72 (0.63–4.72)	0.289
≥ 1 comorbidity (Yes vs No)	7.07 (2.84–17.58)	<0.001

with stage I–II (aOR 12.66, 95% CI 4.81–33.31; $p < 0.001$). TNBC was also associated with higher odds versus HR+/HER2" disease (aOR 4.90, 95% CI 1.54–15.58; $p = 0.007$), whereas HER2+ was not ($p = 0.938$). Presence of ≥ 1 comorbidity increased the odds of RDI <85% (aOR 5.19, 95% CI 2.33–11.56; $p < 0.001$). After adjustment, treatment setting (NAC vs AC) was not independently associated with RDI <85% (aOR 1.36, 95% CI 0.56–3.28; $p = 0.494$).

Predictors of any treatment delays > 7 days

In the adjusted model, older age was associated with higher odds of a delay >7 days (aOR per 10-year increase 2.77, 95% CI 1.76–4.37; $p < 0.001$). Stage III was independently associated with delays compared with stage I–II (aOR 14.48, 95% CI 5.08–41.27; $p < 0.001$). Comorbidity ≥ 1 was also associated with delays (aOR 7.07, 95% CI 2.84–17.58; $p < 0.001$). TNBC showed a non-significant trend toward higher odds of delay (aOR 3.02, 95% CI 0.84–10.84; $p = 0.090$), and HER2+ was not associated ($p = 0.310$). Treatment setting (NAC vs AC) was not significant after adjustment (aOR 1.72, 95% CI 0.63–4.72; $p = 0.289$).

DISCUSSION

Interpretation of differences between the neoadjuvant and adjuvant cohorts must, however, recognise that treatment setting is closely linked to disease stage and tumour biology. This study was designed as a descriptive quality audit rather than a comparative effectiveness trial, and observed NAC–AC differences in relative dose intensity, dose modifications, and toxicity likely reflect a combination of regimen intensity, patient risk, and real-world practice patterns rather than causal effects of treatment sequencing alone.

The neoadjuvant cohort comprised a substantially higher proportion of patients with

more advanced clinical stages and biologically aggressive subtypes, including a greater share of HER2-positive and triple-negative breast cancers. In contrast, the adjuvant group was enriched in more indolent, hormone receptor-positive/HER2-negative tumours (85% vs 55% in NAC). This distribution reflects contemporary practice, in which NAC is preferentially offered to patients with higher tumour burden or aggressive biology.⁸ Patients with HER2-positive or TNBC tumours derive particular benefit from neoadjuvant therapy. These subtypes respond robustly to multi-agent chemotherapy and achieve higher pathologic complete response (pCR) rates, facilitating tumour downstaging and breast-conserving surgery.^{9, 10} In contrast, strongly hormone receptor-positive cancers tend to be less chemosensitive (pCR ~20–30% vs >50% in TNBC),¹⁰ and such patients are more often managed with upfront surgery followed by adjuvant chemotherapy and endocrine therapy, reserving neoadjuvant treatment for selected cases where downstaging is required. These baseline differences underscore that the observed NAC–AC contrasts in dose intensity and toxicity are strongly influenced by underlying disease risk and histological profile rather than treatment sequence alone.

In both settings, an anthracycline–taxane sequence (AC→T) formed the backbone of curative-intent systemic therapy for early breast cancer, accounting for approximately 40–45% of regimens. This pattern reinforces that anthracycline–taxane chemotherapy remains a standard component of curative treatment for many patients with high-risk disease, consistent with multiple randomised trials and meta-analyses demonstrating improved survival when both drug classes are incorporated into adjuvant regimens.¹¹ In the NAC cohort, regimen selection was more intensively tailored to aggressive biology. A

substantial proportion of HER2-positive patients received TCH(P)—typically docetaxel, carboplatin, and trastuzumab with or without pertuzumab. In contrast, only a minority of HER2-positive patients in the adjuvant cohort received a similar combination. This aligns with current practice, in which neoadjuvant protocols for HER2-positive disease increasingly employ dual HER2 blockade (addition of pertuzumab) to maximise response and pCR rates.⁹

In contrast, some lower-risk HER2-positive cases treated adjuvantly may receive single-agent trastuzumab with chemotherapy. Likewise, a notable subset of NAC patients with triple-negative disease received anthracycline- and taxane-based regimens that incorporated carboplatin, reflecting the use of platinum to boost pCR rates based on emerging evidence of its efficacy in this subtype.¹² By contrast, adjuvant treatment more often comprised four cycles of docetaxel–cyclophosphamide, particularly among patients with lower-risk or anthracycline-ineligible profiles, consistent with recognition of TC as an acceptable anthracycline-sparing adjuvant option.¹³

The safety profile of chemotherapy in this cohort was broadly acceptable in both settings, although the neoadjuvant group experienced a somewhat higher burden of acute toxicities. When events were standardised per 100 delivered cycles, rates of grade ≥ 3 neutropenia, febrile neutropenia, grade ≥ 2 peripheral neuropathy, and grade ≥ 2 oral mucositis were modestly higher with NAC than with AC, even though absolute differences were small (for example, 11 vs 10 episodes of severe neutropenia per 100 cycles).^{2, 11, 10} These findings are consistent with the more intensive combination regimens used neoadjuvantly, including carboplatin-containing TCHP and anthracycline–carboplatin sequences, which have been associated with increased haematologic toxicity and higher rates of treatment modification in prior trials and real-world series.^{16, 17}

In our cohort, febrile neutropenia occurred at a rate of 7 per 100 cycles in NAC versus 5 per 100 cycles in AC, which lies within the expected range for dose-dense anthracycline–taxane regimens and contemporary platinum-based combinations [5]. Peripheral neuropathy was also slightly more common during NAC (12 vs 10 events per 100 cycles $\geq$ grade 2), in keeping with

the cumulative neurotoxicity of taxanes, which is a frequent driver of dose reduction or early discontinuation in clinical practice.¹⁸ Overall, these data suggest that neoadjuvant regimens can be delivered safely for most patients, but at the cost of an incrementally higher toxicity burden relative to standard adjuvant therapy.

Our study also demonstrated high adherence to key process-of-care indicators in both settings. Pre-cycle laboratory assessments (full blood count, liver enzymes, and serum creatinine) were documented before the vast majority of chemotherapy administrations, and almost all taxane-containing cycles (approximately 95–96%) had appropriate corticosteroid and antihistamine premedication recorded.¹⁹ Antiemetic prescribing was strongly concordant with emetogenic risk, with 93–96% of highly and moderately emetogenic cycles receiving guideline-consistent prophylaxis. These rates compare favourably with published antiemetic DUEs and registry analyses, where overall concordance is often closer to 70–80% and can fall below 60% in some settings.^{14, 20}

For high–febrile-neutropenia-risk regimens such as dose-dense AC and TCH(P), most eligible patients in our cohort received primary prophylactic G-CSF, and secondary prophylaxis was routinely instituted following neutropenic events, in contrast to reports from other populations in which G-CSF remains underutilised (for example, 38% use in a Puerto Rico registry and only 57% of breast cancer patients ever receiving any G-CSF support).²⁵ Granulocyte-colony-stimulating factors are biological agents that stimulate proliferation, differentiation, and activation of neutrophil precursors, thereby reducing the severity and duration of chemotherapy-induced neutropenia and febrile neutropenia.^{22, 23}

Current clinical practice guidelines, including those from the National Comprehensive Cancer Network, recommend prophylactic G-CSF when the overall FN risk from a chemotherapy regimen is $\geq 20\%$, and to consider it when the risk is 10–20% in the presence of additional patient risk factors.¹⁰ Within this framework, the high adherence to supportive-care and dosing standards observed in our institution—including accurate carboplatin AUC dosing and appropriate body-surface-area capping in high-BSA patients—likely contributed to the manageable safety profile despite

the more intensive regimen use in the neoadjuvant group.²⁴

Older age markedly increased the odds of under dosing; each 10-year increment doubled the odds of RDI < 85%. This is consistent with recent observational evidence showing that women aged >70 years have significantly greater odds of low RDI and worse overall survival than younger counterparts.²⁶ Age related physiologic decline and the higher prevalence of comorbidity likely contribute to treatment interruptions; in a Danish retrospective study, dose reductions and delays were frequently planned at cycle 1 because of comorbid illness and were commonly precipitated by neutropenia or neuropathy. Multivariable modelling from the same study reported that age $\geq$ 65 years and two or more comorbidities increased the odds of RDI < 85% three to five-fold.²

Population based data demonstrate that, among hormone receptor-positive/HER2 negative breast cancers, the proportion with RDI < 85% rises from 20.4 % in stage I to 36.8 % in stage III; for triple negative breast cancer (TNBC), it climbs to 47.2 %.² Advanced disease often requires more aggressive, dose dense regimens and patients may experience cumulative toxicity, leading to more frequent delays or reductions. The odds of RDI < 85 % increased more than five-fold when patients had at least one chronic disease², and similar findings were observed among elderly cohorts where a Charlson Comorbidity Index > 6 predicted low RDI.²⁵

Older age was a strong predictor; for every 10-year age increase the odds of delay more than doubled (aOR 2.77). This is consistent with observations from population-based studies. In the Women's Health Initiative cohort, a delay in adjuvant chemotherapy (>8 weeks) occurred in 23 % of women and was significantly associated with increasing age ($p = 0.004$).²⁸ Ageing is accompanied by reduced bone marrow reserve and organ function, which makes older adults more susceptible to myelosuppression and other toxicities that necessitate treatment postponement. Multicentre geriatric oncology studies also show high rates of dose delays in the oldest patients; in one prospective cohort, 37 % required a dose delay and this was partly attributed to the fact that more than a third of participants were $\geq$ 80 years old.²⁹

Comorbidities further increased the odds of delay (aOR 7.07). A systematic review of older cancer patients reported that unplanned delays >1 week were significantly related to a history of comorbidities; diabetes, hypertension and elevated Charlson comorbidity index scores were predictors of treatment delay, and age was also highlighted as a risk factor.³⁰ Similarly, in the Women's Health Initiative analysis, higher Charlson comorbidity scores were associated with delays to chemotherapy and radiation.²⁸ Comorbidities may impair organ function or require medications that interact with chemotherapy, leading clinicians to postpone treatment for stabilization.

These findings emphasise the need for proactive supportive care. Comprehensive geriatric assessment and optimization of comorbid conditions, use of growth factor support and multidisciplinary coordination may help older or comorbid patients maintain dose intensity. For patients with advanced disease, careful management of toxicities and treatment planning are crucial, because delays may compromise disease control.

This study has several limitations that should be considered when interpreting the findings. It was a single-centre, observational drug-utilization evaluation conducted over 12 months with two cohorts of 100 patients each; therefore, external generalisability may be limited to institutions with similar patient case-mix, regimen selection, and supportive-care infrastructure. Although analyses were primarily descriptive, the multivariable logistic models (for suboptimal RDI and for delays >7 days) remain subject to residual confounding and cannot establish causal relationships between baseline factors and delivery outcomes because treatment setting and regimen intensity are inherently linked to stage and tumour biology. Data were abstracted from routine clinical documentation; consequently, under-documentation, particularly of lower-grade or patient-reported toxicities, is possible despite CTCAE-based grading, and misclassification of events or process metrics cannot be excluded. Finally, patients with incomplete medical, chemotherapy, or laboratory records were excluded, which may introduce selection bias if documentation quality was associated with delivery performance or toxicity.

CONCLUSION

In this single-centre drug-utilization evaluation of 200 women with early breast cancer, neoadjuvant chemotherapy was preferentially used for higher-risk disease and included more HER2-directed and platinum-containing regimens. Delivered cycles matched planned cycles, but more intensive regimens—particularly in the neoadjuvant setting—showed lower mean relative dose intensity and higher rates of dose reductions and >7-day delays than adjuvant therapy. Neutropenia remained the most frequent safety event, and febrile neutropenia occurred more often during neoadjuvant treatment. Despite these challenges, quality-of-care indicators were consistently high in both cohorts, including timely pre-cycle laboratories, antiemetic guideline concordance, appropriate primary/secondary G-CSF use, accurate carboplatin AUC dosing, and adherence to body-surface-area capping. In adjusted analyses, older age, stage III disease, and comorbidity burden predicted suboptimal delivery and delays, identifying patients who may benefit from targeted supportive-care escalation. Future multicentre prospective studies should link delivery metrics to pCR, recurrence, and survival and test pharmacist-led, risk-adapted interventions and remote monitoring.

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Conflict of interest

The authors do not have any conflict of interest.

Data Availability Statement

The data will be made available upon reasonable request to the corresponding author.

Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki. The study was

reviewed and approved by the Institutional Ethics Committee (VIPT/IEC/549/2025).

Informed Consent Statement

Written informed consent was obtained from participating patients.

Clinical Trial Registration

This research does not involve any clinical trials.

Permission to reproduce material from other sources

Not Applicable.

Author Contributions

Conceptualization, Data Collection: Vinod Kumar Mugada; Supervision: Vidaydhara Suryadevara; Data Analysis, Manuscript Writing, Editing, Proofreading, and Final Approval: Vinod Kumar Mugada, Vidaydhara Suryadevara.

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