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'ADVANCE' (A Pilot Trial) ADjuVANt Chemotherapy in the Elderly: Developing and Evaluating Lower-Toxicity Chemotherapy Options for Older Patients with Breast Cancer

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Abstract

Introduction: Older adults with breast cancer receiving neo/adjuvant chemotherapy are at high risk for poor outcomes and are underrepresented in clinical trials. The ADVANCE (ADjuVANt Chemotherapy in the Elderly) trial evaluated the feasibility of two neo/adjuvant chemotherapy regimens in parallel-enrolling cohorts of older patients with human epidermal growth factor receptor 2-negative breast cancer: cohort 1—triple-negative; cohort 2—hormone receptor-positive.

Materials and Methods: Adults age ≥70 years with stage I-III breast cancer warranting neo/adjuvant chemotherapy were enrolled. Cohort 1 received weekly carboplatin (area under the curve 2) and weekly paclitaxel 80 mg/m^2 for twelve weeks; cohort 2 received weekly paclitaxel 80 mg/m^2 plus every-three-weekly cyclophosphamide 600 mg/m^2 over twelve weeks. The primary study endpoint was feasibility, defined as ≥80% of patients receiving ≥80% of intended weeks/doses of therapy. All dose modifications were applied per clinician discretion.

Results: Forty women (n=20 per cohort) were enrolled from March 25, 2019 through August 3, 2020 from three centers; 45% and 35% of patients in cohorts 1 and 2 were age >75, respectively. Neither cohort achieved targeted thresholds for feasibility. In cohort 1, eight (40.0%) met feasibility (95% confidence interval [CI]=19.1–63.9%), while ten (50.0%) met feasibility in cohort 2 (95% CI=27.2–72.8). Neutropenia was the most common grade 3–4 toxicity (cohort 1—65%, cohort 2—55%). In cohort 1, 80% and 85% required ≥1 dose holds of carboplatin and/or paclitaxel, respectively. In cohort 2, 10% required dose hold(s) for cyclophosphamide and/or 65% for paclitaxel.

Discussion: In this pragmatic pilot examining chemotherapy regimens in older adults with breast cancer, neither regimen met target goals for feasibility. Developing efficacious and tolerable regimens for older patients with breast cancer who need chemotherapy remains an important goal.

Keywords

Chemotherapy; older adults; breast cancer; carboplatin; paclitaxel; cyclophosphamide

INTRODUCTION

The incidence of breast cancer among older women is rising,[1] and one-third of all breast cancer diagnoses occur in those aged ≥70 years.[2] Although most older patients with breast cancer present with favorable hormone receptor-positive (HR+) tumor subtypes[3] and early stages of disease,[4,5] the breast cancer-specific outcomes for older patients are often less favorable than those in younger women, despite significant competing causes of death.[4–7] For women aged ≥70 years in particular, survival improvements over time have occurred at a slower pace compared with younger women,[8] and older patients experience lower breast cancer-specific survival regardless of breast cancer stage and subtype, including those with both HR+ and triple-negative (TN) disease.[9] Many factors lead to worse outcomes in older patients, including comorbid illness, undertreatment, treatment-related toxicity, early discontinuation of hormonal therapy, and variable disease biology.

Approximately 80% of breast cancers in those aged ≥70 years are HR+, while a substantial minority are TN (approximately 10% or ≅7,000 cases/year).[3,9] Although adjuvant hormonal therapy is sufficient systemic treatment in the setting of lower-risk HR+ disease, a considerable proportion of older patients with higher-risk HR+ or TN breast cancer may benefit from chemotherapy. However, when toxicity or comorbidity concerns are paramount, older patients are in jeopardy of undertreatment and/or receipt of non-guideline concordant care[10–12] because they lack clear alternatives to standard chemotherapy. In the setting of TN disease in particular, older patients do not have non-chemotherapy systemic therapy options and often do not receive treatment.[13,14]

The most frequently prescribed and often preferred adjuvant chemotherapy regimen in older patients with human epidermal growth factor receptor 2 (HER2)-negative breast cancer is docetaxel-cyclophosphamide (TC).[15–17] However, nearly 50% of those aged ≥65 develop grade ≥ 3 adverse events during their chemotherapy course,[15,18] with hospitalizations[11,16] and functional decline experienced by many.[15,18] Despite trials of alternative therapeutic approaches for older patients,[19,20] no regimen has demonstrated sufficient efficacy and tolerability to replace standard combination chemotherapy, and most patients eventually complete TC, even when toxicity is observed.[15]

This pilot study, designed for older adults with breast cancer, prospectively evaluated the feasibility of two potential regimens for neo/adjuvant chemotherapy. The goal was to provide preliminary data to support the design of a larger clinical trial for older patients at higher risk for poor outcomes and who are underrepresented in clinical trials.

MATERIALS AND METHODS

Study Overview (Figure 1)

In the ADVANCE (ADjuVANt Chemotherapy in the Elderly) trial, we evaluated the feasibility of administering chemotherapy in two simultaneously-enrolling cohorts of 20 patients for those age ≥70 years who were recommended by their clinicians to receive neoadjuvant or adjuvant chemotherapy for HER2-negative breast cancer. In cohort 1 (TN cohort), planned treatment included weekly carboplatin-paclitaxel for twelve weeks. In cohort 2 (HR+), planned treatment included every-three-week cyclophosphamide plus weekly paclitaxel for twelve weeks, adapted from traditional TC,[21] with weekly paclitaxel in place of every-three-week docetaxel.[22]

Patient Eligibility

Study eligibility included consenting patients aged ≥70 years, with histologically confirmed, non-metastatic, HER2-negative invasive breast cancer.[23] This study was approved by the institutional review boards of each participating site prior to enrollment of participants (DFCI protocol #19–031). All patients provided written informed consent and the study was carried out in accordance with the Declaration of Helsinki.

Tumors with immunohistochemistry staining of <10% for estrogen receptor (ER) and progesterone receptor (PR), per local pathology review, were considered TN and these patients were assigned to cohort 1; tumors with ≥10% staining for ER and/or PR were

considered HR+ and patients were assigned to cohort 2. Patients were advised to receive neoadjuvant or adjuvant chemotherapy by their treating oncologist. Any additional cancer treatment including breast and nodal surgery, radiation, or hormonal therapy was at the discretion of the treating provider but could not be administered concurrently with study therapy. Patients could receive additional chemotherapy (e.g., anthracycline or post-neoadjuvant capecitabine) if delivered after any study-related chemotherapy. There were no specific requirements for life expectancy, performance status, or laboratory criteria.

Key study exclusions included prior chemotherapy received for the current cancer. Patients initially receiving preoperative hormonal therapy who were then recommended for adjuvant chemotherapy remained eligible, and hormonal therapy was held during study treatment. Prior breast cancer diagnoses were allowed, provided that the treating clinician deemed the current cancer to represent a new primary breast cancer and not recurrent disease. Prior chemotherapy was allowed in the setting of other/prior cancers, with exception of prior carboplatin (cohort 1), cyclophosphamide (cohort 2), or paclitaxel (both cohorts) receipt in the last two years.

Selection of Regimens

Carboplatin-paclitaxel (cohort 1)—In breast cancer, neo/adjuvant carboplatin and paclitaxel have been widely examined in clinical trials when combined sequentially with other agents, such as anthracycline- and alkylating-based therapies in GeparSixto,[24] Cancer and Leukemia Group B (CALGB) 40603,[25] and GEICAM.2006–003.[26] However, there are increasing data supporting the use of platinum and taxanes as primary therapy for those with TN disease, such as a trial administering neoadjuvant carboplatin-docetaxel where pathological complete response rates were high.[27] In another study of patients with locally advanced breast cancer of various subtypes, 80% of tumors had some degree of response to taxane plus carboplatin with a relatively low incidence of grade ≥3 toxicity.[28] Although no study has directly compared the efficacy and toxicity of every-three-weekly vs. weekly carboplatin in the adjuvant setting, once per week dosing is a well-established method of administration and is ‘titratable’ week-to-week. There are also data using weekly carboplatin-paclitaxel in the setting of metastatic breast and lung cancer, demonstrating activity and tolerability.[29–32] Further, while ADVANCE was underway, additional promising efficacy data[33] with adjuvant carboplatin-paclitaxel were published, adding further support for its use.

Cyclophosphamide-paclitaxel (cohort 2)—Adjuvant TC is a well-established adjuvant breast cancer regimen[21] and is frequently administered to older patients to completion.[15,16] To develop a regimen with similar efficacy but perhaps better tolerability, we selected a weekly paclitaxel-based regimen (rather than every-three-week docetaxel) as the therapeutic partner for cyclophosphamide. First, weekly taxane may offer better therapeutic efficacy than every-three-weekly taxane.[22,34,35] Second, though paclitaxel and docetaxel have similar efficacy, paclitaxel may have more favorable tolerability.[22,36,37] However, it is of note that dosing of docetaxel in these cited studies was higher than that used in modern-era TC, and growth factor was not systematically applied. Third, although formal neo/adjuvant evaluations of our ‘modified TC’ have not been conducted, taxane

plus cyclophosphamide are standard agents in multiple regimens, with well-established tolerability and efficacy.[38] Further, a similar modified TC regimen was evaluated in the metastatic setting in a small study, and we thus planned a regimen of weekly paclitaxel 80 mg/m2 and every-three-week cyclophosphamide 600 mg/m2.[39] Other small studies in metastatic disease have also examined alternative taxane-cyclophosphamide regimens demonstrating tolerability and preliminary efficacy.[40–42]

Treatment Administration

Cohort 1 participants initiated twelve consecutive weeks of commercially supplied, weekly carboplatin dosed at area under the curve (AUC) 2 and paclitaxel 80 mg/m^2. Cohort 2 participants initiated weekly paclitaxel 80 mg/m^2 plus standard dose cyclophosphamide 600 mg/m^2 every three weeks over twelve consecutive weeks. Cycles in both cohorts were three weeks, with a total of four cycles planned. Treatments were administered intravenously per institutional guidelines without planned breaks, unless clinically indicated. There were no mandated laboratory requirements or growth factor use; this was left to clinician discretion.

During treatment, protocol guidance was provided on when to consider dose modifications/holds for the offending agent for grade ≥3 toxicity (other than alopecia) or a clinically significant grade 1–2 toxicity. However, clinicians could proceed with treatment as they felt appropriate, including any treatment modifications/omissions, with make-up doses allowed to complete up to four full cycles of treatment. In the absence of treatment delays due to adverse event(s) or unacceptable toxicity, treatments continued until completion of protocol-defined therapy, disease progression, intercurrent illness that prevented further treatment, or participant preference.

Study visits occurred on day 1 of each cycle; toxicities were graded using the revised National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. During treatment, we collected information on treatment delays, omissions, and modifications. After therapy completion, additional study visits at three months and one year allowed for collection of information on longer-term toxicity, recurrence, and vital status; medical record review was allowed for up to two years. To inform future correlative analyses, archived tissue was collected at baseline and sequential research blood samples for correlative endpoints were collected for all enrolled patients (data forthcoming).

Survey Instruments

Additional patient assessments included a geriatric assessment (GA)[43–46] and frailty (Rockwood Index)[47] at baseline, cycle three day one, end-of-treatment, three months post-treatment [+/− one month], and twelve months post-treatment [+/− one month]). We also collected patient-reported outcomes (PROs) using the NCI PRO-CTCAE grading system[48] at baseline, day one of each cycle, end-of-treatment, and three months post-treatment [+/− one month].

At baseline, clinicians were surveyed via email about estimations for the likelihood of severe toxicity for that patient, the type of toxicities anticipated, and if having GA information was useful. All patient and clinician surveys are provided in the supplemental file.

Statistical Analysis

The primary study endpoint was feasibility for each cohort, defined as ≥80% of patients receiving ≥80% of intended therapy, in order to align with historical studies which suggest an impact on outcome if <85% relative dose intensity is administered.[49] To meet study feasibility, participants in each cohort had to receive ≥ ten weeks of scheduled therapy including up to two dose modification 'events.' This was defined as having up to two holds/reductions in total (i.e., one dose change for one agent or two dose changes/delays for one agent). Any patient who received one dose of study treatment was considered evaluable, and any patient who registered but never started therapy was replaced, for a goal of 40 evaluable patients. Feasibility would be achieved if the upper bound of a two-sided 90% confidence interval (CI) using the exact binomial methods covered an 80% response rate, which was consistent with observing 29 patients meeting feasibility requirements among the 40 patients enrolled.

Secondary endpoints include the proportion of patients with NCI CTCAE version 5.0. toxicities, dose modifications, treatment omissions, or early discontinuation of the therapy within each cohort. We also present the toxicity predictions from clinician surveys at baseline and how these aligned with CTCAE-graded toxicities. Finally, we examined whether clinicians found the baseline GA information useful. Given small sample sizes, all secondary outcomes are descriptive and exploratory. Longer-term clinical endpoints and biological correlatives will be reported separately.

RESULTS

Forty women enrolled between March 25, 2019 and August 3, 2020 at three centers (Dana-Farber Cancer Institute, Boston, MA, and its satellite practices in Milford and Weymouth [both in MA]; City of Hope Duarte, CA; and Novant Health Cancer Institute, Kernersville, NC). The median age of study participants was 75 years (range 69–83) in cohort 1 and 74 years (range 69–86) in cohort 2 (one woman in each cohort was allowed to enroll within six months of her 70th birthday).

Table 1[47] displays participant characteristics by study cohort; 15% were non-White, 60–70% were born in the US. In cohort 1, 35%, 45%, and 15% had stage I, II, III disease, respectively. In cohort 2, 25%, 35%, and 35% of participants had stage I, II, and III disease, respectively; 60% of participants in both cohorts received treatment in the adjuvant (as opposed to neoadjuvant) setting. At baseline, only 20% in cohort 1 and 5% in cohort 2 met criteria for frailty (Table 2).[47,50–56] Despite their ages, most patients had a high degree of physical function and independence as self-reported in measures of daily living and social support, with infrequent falls in the last six months.

Feasibility (Figure 2 and Supplemental Table S1)

The thresholds for treatment feasibility were not met for participants in cohort 1 or cohort 2. In cohort 1, eight (40.0%) of patients met feasibility endpoints for weekly carboplatin-paclitaxel therapy (95% CI=19.1–63.9%), while ten (50.0%) patients met criteria in cohort 2 (95% CI=27.2–72.8). In cohort 1, sixteen (80%) required ≥1 carboplatin dose hold (range

0–5 dose holds per patient), and seventeen (85%) required ≥1 paclitaxel dose hold (range 0–5 dose holds per patient). This resulted in a total duration of any administered therapy of five to sixteen weeks, with seven (35%) receiving < ten doses of carboplatin and six (30%) patients receiving < ten doses of paclitaxel over that period. In addition, dose reductions were applied in twelve (60%) for carboplatin and thirteen (65%) for paclitaxel. Overall, eleven (55%) met feasibility criteria for carboplatin and ten (50%) for paclitaxel, with eight (40%) patients meeting criteria for both treatments, as above. The reasons for discontinuation of therapy in cohort 1 included therapy complete (n=14, 70%), unacceptable toxicity or clinician discretion due to toxicity (n=4, 20%), and patient withdrawal (n=2, 10%).

In cohort 2, the maximum possible doses of cyclophosphamide were four because it was administered every three weeks. Overall, two (10%) had cyclophosphamide doses held (one hold for each), and dose reductions were applied for five patients (10%; three times in one patient, one to two times in others). For paclitaxel in this cohort, thirteen (65%) had doses held (range 0–4 doses held per patient) and ten (50%) had dose-reductions applied. This resulted in a duration of therapy of one to sixteen weeks, and three (15%) participants did not complete ≥10 weeks of therapy (one participant withdrew after one dose of paclitaxel and cyclophosphamide, and two patients stopped study treatment after four and nine weeks due to toxicity). Overall, sixteen (80%) patients met feasibility for cyclophosphamide, ten (50%) for paclitaxel, and ten for both treatments (50%), as above. The reasons for study treatment discontinuation in cohort 2 included treatment completed (n=16, 80%), patient withdrawal (n=2, 10%), and unacceptable toxicity (n=2, 10%).

Toxicity

Grade 2 and higher toxicities observed and deemed related to any study treatment are shown in Table 3 (cohort 1) and Table 4 (cohort 2). There were no treatment-related deaths or unexpected toxicities observed.

In cohort 1, the most common grade 2–4 toxicity was neutropenia, with 10%, 45%, and 20% of patients having grade 2, 3, and 4 neutropenia, respectively. One patient had grade 3 febrile neutropenia. No other grade 4 events were observed. Fatigue was also reported as grade 2 in 50% of patients and grade 3 in 5%. Neuropathy was reported as grade 2 only and occurred in 35% of patients.

In cohort 2, neutropenia was also commonly reported and was observed as grade 3 in 15% and grade 4 in 40% of patients. Febrile neutropenia grade 3 and 4 events occurred in 5% and 10% of patients, respectively. Neuropathy occurred as grade 2 only (in 10% of patients), and fatigue was reported as grade 2 in 25% and grade 3 in 5%. One patient (5%) developed grade 3 pneumonitis.

Over the course of treatment, four (20%) and eight (40%) patients in cohorts 1 and 2, respectively, received myeloid growth factor support, administered per clinician discretion. Patients had functional setbacks with treatment in both cohorts; the proportion of patients categorized as frail[47] at end of treatment visits was numerically higher in both cohorts (vs. baseline), with 30% (from 20%) of patients in cohort 1 and 15% (from 5%) in cohort 2.

Clinician surveys

At baseline, 30 clinician surveys were submitted that estimated likelihood of grade ≥3 toxicity during chemotherapy for their patient. Responses included the following for likelihood of toxicity: >60% (n=1), 41–60% (n=1), 21–40% (n=8), 10–20% (n=15), or ≤10% (n=5). The most frequently anticipated toxicities (not mutually exclusive; clinicians could select up to three) were neutropenia (n=22), neuropathy (n=17), fatigue (n=17), anemia (n=14), and thrombocytopenia (n=7).

Among the 29 clinicians responding to the surveys on the utility of summary GA, 24 (82.8%) stated they reviewed the summary results provided over email, and sixteen (55.2%) found the information useful; eleven additional clinicians stated they were not sure if the information was helpful and two stated it was not helpful. In just over 10% of surveys, clinicians reported that the information from the GA resulted in “some change(s) in management or referrals they would not have otherwise made, even if something minor.”

DISCUSSION

Older patients with breast cancer need prospective evidence to guide treatment decisions and to improve upon existing chemotherapy-based options, which have a high degree of toxicity and risk for functional decline. In this pilot study evaluating twelve weeks of combination neo/adjuvant carboplatin-paclitaxel or cyclophosphamide-paclitaxel as potential chemotherapeutic options, neither regimen met pre-specified thresholds for feasibility. However, despite a high degree of neutropenia requiring treatment modifications, treatments were otherwise well tolerated, and most (70% cohort 1, 80% cohort 2) eventually completed protocol therapy, in line with other studies administering similar regimens.[25,33,57,58] This may be due to the fact that myelosuppression can be an asymptomatic adverse event discovered by laboratory testing alone. Interestingly, on baseline surveys, clinicians in our study underestimated the likelihood of toxicity but aligned well with the types of toxicities observed, further emphasizing the value of including objective measures to predict toxicity in older adults.[15] Future analyses from our study will evaluate PROs, their agreement with clinician-reported toxicity, and longitudinal assessments of the GA, which will better inform tolerability and the impact on quality of life from the patient perspective.

Prior studies administering similar regimens also report myelosuppression as the most common adverse event.[21,25,33,39,57–60] In our study, the proportion of grade 3–4 neutropenia observed was comparable or lower than observed in some studies (not limited to older patients) with similar agents,[33,57,58] but was higher than other studies where mandatory myeloid growth factor and/or different schedules of treatment were utilized.[15,25,57] In addition, the frequency of dose reductions was higher in our study than reported previously for similar regimens, though past studies have not typically reported the same degree of detail for dose modifications and dose holds, and there is variability in platinum dosing schedules and taxane agents.[25,33,57,59,60] For example, in the carboplatin-paclitaxel arm of Sikov et. al.’s neoadjuvant study[25] carboplatin was dosed every three weeks, with 60% of participants receiving 11–12 doses of paclitaxel and 25% receiving 9–10 doses, perhaps a higher dose intensity than seen in our study, though additional information on dose reductions was not reported in detail.

There are several possible reasons why the regimens tested in our study did not prove feasible, some of which are related to study limitations. First, our thresholds for feasibility were strict, limiting the likelihood of reaching our endpoint. Given the lack of standard definitions for feasibility across studies,[61,62] our definitions for feasibility were pragmatically selected based on historical data suggesting a threshold of 85% of intended dose intensity to maintain efficacy.[49] However, data on optimal chemotherapy dosing for older patients are limited and several studies with carboplatin and taxanes report frequent dose modifications with preservation of benefit.[25,33,57–60] Second, because the study design intended to promote a real-world assessment of treatment in academic and community oncology settings, we did not mandate dose reductions or growth factor use (less than 50% of patients received growth factor), and clinicians adjusted treatments according to their comfort, judgment, and practice style. Given the weekly schedule of therapy, patient chemotherapy schedules were busy, and clinicians had regular opportunities to adapt treatment plans and did so readily. As evidence of this, in cohort 2, all but one patient received all four doses of cyclophosphamide, and weekly paclitaxel administration was the limiting agent for feasibility, with five patients receiving < ten doses of paclitaxel. In addition, study enrollment occurred during the peak of the COVID-19 pandemic, and this may have impacted clinician thresholds for treatment modification and cessation.

Other attempts to develop effective, tolerable, and pragmatic alternatives to standard chemotherapy regimens for older adults with HER2-negative breast cancer[19,20,63] have also highlighted challenges with tolerability. In future explorations to develop regimens in this context, considerations for up-front dose reductions, mandated use of myeloid growth factor, treatment breaks (e.g., treating three weeks on/one week off), or improved supportive care may promote safety and tolerability while maintaining dose intensity. As an example, the upcoming multi-center DOROTHY trial (Dose Reduction of doceTaxel-based cHemotherapY) in vulnerable older adults with early breast cancer will be evaluating a starting dose reduction of docetaxel (vs. standard dosing) as part of TC, with the goal to maintain dose intensity without sacrificing efficacy. Another future approach would be to further explore single-agent, sequential treatment strategies, known to be as effective as combination regimens but less toxic.[38]

We recognize additional study limitations. Although the pragmatic nature and multi-center and multi-geographical presence of this trial was a strength (with 15% non-White participants and 30–40% born outside the US), clinician flexibility and the small samples sizes for each cohort limited interpretability. In addition, we did not incorporate immunotherapy into preoperative management for TN disease given the timing of presentation and publication of the KEYNOTE-522 study,[64,65] though at least 35% of patients (those with stage I disease) with TN breast cancer on study would not have met the conditions for immunotherapy receipt. Further, given the pilot nature of this study, treatment efficacy data were not included as a study endpoint, though we will explore outcomes at two years of follow-up for all study participants.

In summary, this study directly addressed gaps in knowledge by obtaining pilot, prospective data on the feasibility of two potential neo/adjuvant chemotherapy treatment options for older patients with breast cancer. These patients were anticipated to significantly benefit

from neo/adjuvant chemotherapy, with the majority completing protocol therapy; however, this study did not meet feasibility endpoints. There is significant national momentum to increase clinical trial participation for older adults with cancer and advance the evidence base for treatments. We demonstrated proof-of-concept that chemotherapy-based trials for older adults are urgently needed and can enroll to completion through strong multi-center collaborations. Our results underscore the need for deeper insights into how best to treat older patients with breast cancer. Developing efficacious and tolerable regimens remains a priority for this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement:

Data are available from the authors, upon reasonable request.

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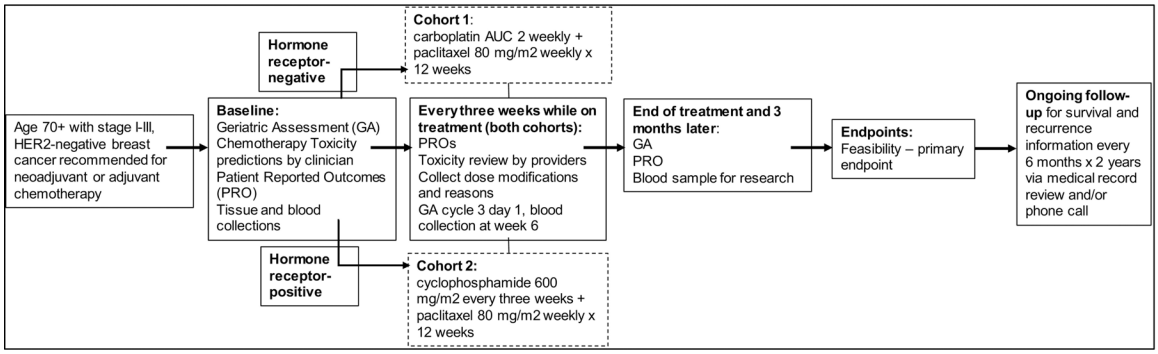

Figure 1.

Study Schema

HER-2, human epidermal growth factor receptor 2; AUC, area under the curve

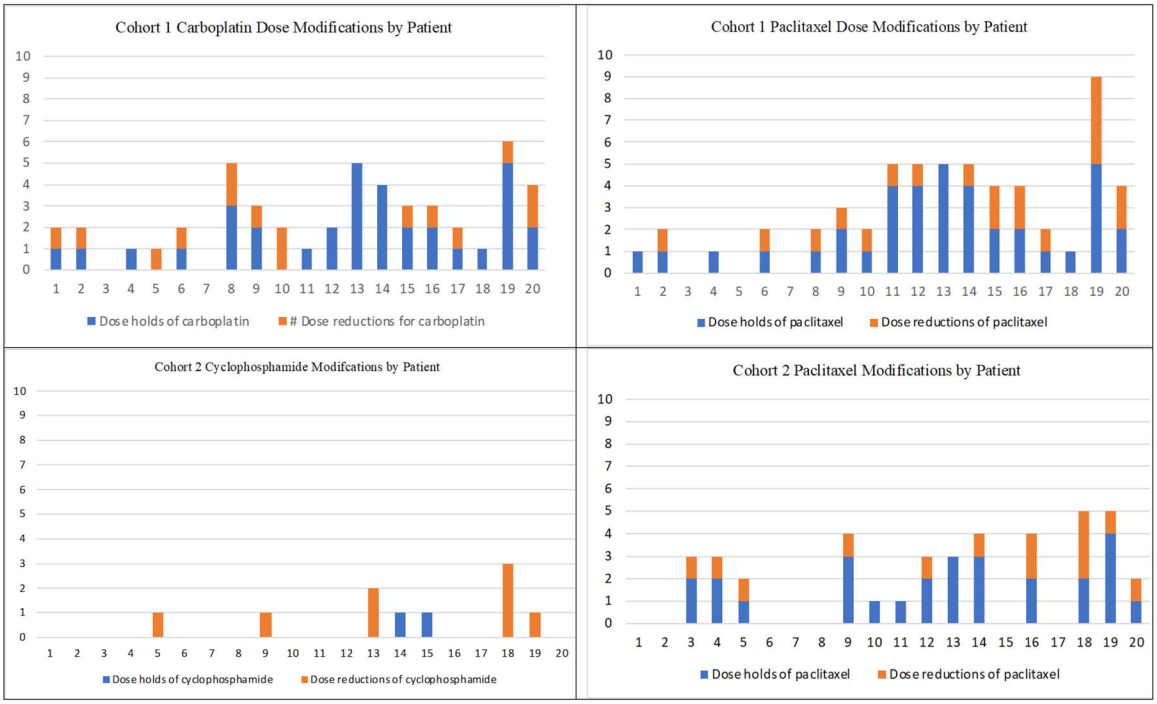

Figure 2.

Dose modifications per patient (1–20) in each cohort by agent (A=cohort 1, carboplatin; B=cohort 1, paclitaxel; C=cohort 2, cyclophosphamide; D=cohort 2, paclitaxel). In all graphs, the Y axis represents frequency of dose holds or reductions. The x-axis represents individual patients in each cohort (1–20).

Table 1.

Participant Characteristics by Cohort

Characteristic	Cohort 1 (triple-negative; n=20) (n, %)	Cohort 2 (hormone receptor- positive; n=20) (n, %)
Age (years)		
69–75	11(55)	13(65)
76–80	7(35)	6(30)
≥81	2(10)	1(5)
Median age (range)	74.5(69–83)	73.5(69–86)
Baseline frailty score[a]		
Robust (0–0.2)	8(40)	18(90)
Pre-frail (>0.2–0.35)	6(30)	1(5)
Frail (>0.35)	4(20)	1(5)
Not done	2 (10)	0 (0)
Female	20(100)	20(100)
Non-White race	3(15)	3(15)
Hispanic ethnicity	2(10)	1(5)
Born in U.S[b]	14(70)	12(60)
Highest educational attainment	5(25)	3(15)
High school graduate or less	6(30)	2(10)
Some college or tech school	7(35)	8(40)
College or higher	2(10)	7(35)
Not answered		
Income		
Less than $20,000	1(5)	1(5)
$20,000 to $40,000	4(20)	1(5)
$40,001 to $60,000	2(10)	3(15)
$60,001 to $80,000	1(5)	5(25)
$80,001 or more	5(25)	2(10)
I prefer not to answer	4(20)	1(5)
Missing income / did not answer	3 (15)	7 (35)
Married/with domestic partner	6(30)	6(30)
Household composition		
Lives alone	4(20)	5(25)
Lives with someone	14(70)	8(40)
Not answered	2(10)	7(35)
With whom do you live?		
Alone	4(20)	5(25)
Spouse/partner +/− children	6(30)	5(25)
A child/children	6(30)	1(5)
A friend	1(5)	--

Characteristic	Cohort 1 (triple-negative; n=20) (n, %)	Cohort 2 (hormone receptor- positive; n=20) (n, %)
Other relative	1(5)	2(10)
Not answered	2(10)	7(35)
Location of residence		
Urban	2(10)	3(15)
Suburban	14(70)	6(30)
Rural	2(10)	4(20)
Not answered	2 (10)	7(35)
Employment		
Employed	3(15)	3(15)
Retired/not working	15(75)	10(50)
Not answered	2(10)	7(35)
Stage of disease[c]		
I	7(35)	5(25)
II	9(45)	7(35)
III	3(15)	7(35)
Not classified	1(5)	1(5)
Treatment setting		
Neoadjuvant	8(40)	8(40)
Adjuvant	12(60)	12(60)

[a] Rockwood Index[47]

[b] Countries of birth outside the US included Ireland, Mexico, Pakistan, and Portugal. The first language reported across both cohorts was English for all women except for 1 Portuguese, 1 Urdu, and 1 Spanish.

[c] Stage is presented as clinical stage if a patient received neoadjuvant therapy and pathological if a patient received adjuvant therapy

Table 2.

Geriatric Assessment Findings at Baseline by Cohort

Baseline Geriatric Assessment Domains		**Cohort 1 (triple-negative; n=20) (n, %)**		**Cohort 2 (hormone receptor-positive; n=20) (n, %)**	
	Description	***Mean (SD)***	***Median (range)***	***Mean (SD)***	***Median (range)***
Functional status					
ADLs (Medical Outcomes study [MOS]) subscale[50]	Measures limitations in physical function	68.8(29)	75.0(5.0–100)	77.7(21.8)	85.0(35–100)
Instrumental Activities of Daily Living (IADLs) using Older American Resources and Services (OARS) subscale[51]	Measures ability to complete activities to maintain independence	12.8(1.7)	14.0(9.0–14.0)	13.8(0.4)	14.0(13–14)
Falls	Number with at least 1 fall in last 6 months (%)	--	3(15%)	--	3(15%)
Karnofsky performance status (by study staff)[52]	Global scale for patient function (0–100)	92.9(6.9)	90(80–100)	93.9(8.5)	100(70–100)
Timed up and go[53] (seconds) (by study staff)	Time it takes for individual to stand up, walk 10 feet, return to chair, and sit back down (>12 seconds is at risk for falls)	11.8(4.1)	11.0(4–22)	11.4(3.6)	11.0(6–19.8)
Comorbidity OARS physical health scale[51]	Assesses the presence of 13 comorbid conditions and effect of illness on daily activities	3.2(1.7)	3.0(0–6)	15(1.3)	1.0(0–4)
Psychological state Mental health inventory[54]	Evaluates level of depression and anxiety in the last month	80.1(16.4)	82.4(40.0-100)	78.6(12.5)	82.2(56.9–97.3)
Social activity[54,55]		62.3(17.2)	66.7(25.0-83.3)	57.7(20.3)	58.3(16.7–83.3)
MOS social support (Overall)	Overall score	90.4(12.0)	97.9(68.8-100)	87.3(15.3)	91.7(52.1–100)
MOS social support (tangible subscale)	Evaluates the self-reported availability of tangible/physical support	87.9(16.0)	93.8(56.3-100)	88.9(16.6)	100(43.8–100)
MOS social support (emotional/informational subscale)	Evaluates the self-reported availability of emotional/ informational support	91.7(12)	100(68.8–100)	86.5(18.1)	90.6(37.5–100)
Nutrition					
Body mass index	Weight (kg) / height (m^2)	28.5(5.3)	27.9(20.4–41.7)	30.9(6.1)	30.5(23.4–47.1)
Weight loss	% with ≥5% unintentional weight loss in last 6 months	2(10%)	1(5%)	2(10%)	1(5%)
Cognition (Blessed Orientation Memory Concentration[56] (% with <11)	Cognitive assessment, score ≥11 represents impairment	16(80%)	3(15%)	19(95%)	1(5%)

ADLs, Activities of Daily Living; IADLs, Instrumental Activities of Daily Living; OARS, Older American Resources and Services

Table 3.

Adverse events related to either chemotherapy in the triple-negative cohort (cohort 1) (n, %)

Toxicity	Grade 2	Grade 3	Grade 4
Neutrophil count decreased	2(10)	9(45)	4(20)
White blood cell decreased	2(10)	3(15)	--
Fatigue	10(50)	1(5)	--
Peripheral sensory neuropathy	7(35)	--	--
Anemia	3(15)	3(15)	--
Alopecia	5(25)	--	--
Diarrhea	2(10)	2(10)	--
Infusion related reaction	4(20)	--	--
Nausea	4(20)	--	--
Dysgeusia	3(15)	--	--
Hyponatremia	2(10)	1(5)	--
Mucositis oral	3(15)	--	--
Constipation	2(10)	--	--
Creatinine increased	2(10)	--	--
Generalized muscle weakness	1(5)	1(5)	--
Platelet count decreased	2(10)	--	--
Rash acneiform	1(5)	1(5)	--
Urinary tract infection	2(10)	--	--
Alanine aminotransferase increased	1(5)	--	--
Anorexia	1(5)	--	--
Arthralgia	1(5)	--	--
Aspartate aminotransferase increased	1(5)	--	--
Blood bilirubin increased	1(5)	--	--
Blurred vision	1(5)	--	--
Chills	1(5)	--	--
Dehydration	1(5)	--	--
Dry mouth	1(5)	--	--
Dyspepsia	1(5)	--	--
Dyspnea	--	1(5)	--
Enterocolitis infectious	--	1(5)	--
Fall	1(5)	--	--
Febrile neutropenia	--	1(5)	--
Gastroesophageal reflux disease	1(5)	--	--
Gastrointestinal disorders - Other, specify	1(5)	--	--
Insomnia	1(5)	--	--
Myalgia	1(5)	--	--
Paresthesia	1(5)	--	--

Toxicity	Grade 2	Grade 3	Grade 4
Pruritus	1(5)	--	--
Rash maculo-papular	1(5)	--	--
Skin infection	--	1(5)	--
Vaginal dryness	1(5)	--	--
Vomiting	1(5)	--	--
Weight loss	1(5)	--	--

Table 4.

Adverse events related to either chemotherapy in the hormone receptor-positive cohort (cohort 2) (n, %)

Toxicity	Grade 2	Grade 3	Grade 4
Neutrophil count decreased	--	3(15)	8(40)
White blood cell decreased	2(10)	4(20)	2(10)
Alopecia	7(35)	--	--
Fatigue	5(25)	1(5)	--
Anemia	4(20)	1(5)	--
Lymphocyte count decreased	3(15)	2(10)	--
Diarrhea	3(15)	--	--
Febrile neutropenia	--	1(5)	2(10)
Peripheral sensory neuropathy	2(10)	--	--
Urinary tract infection	1(5)	1(5)	--
Anorexia	1(5)	--	--
Arthralgia	1(5)	--	--
Concentration impairment	1(5)	--	--
Constipation	1(5)	--	--
Generalized edema	--	1(5)	--
Hypoalbuminemia	1(5)	--	--
Mucositis oral	1(5)	--	--
Nausea	1(5)	--	--
Papulopustular rash	1(5)	--	--
Pneumonitis	--	1(5)	--
Rash maculo-papular	1(5)	--	--