Published in final edited form as:

Breast J. 2018 July ; 24(4): 610–614. doi:10.1111/tbj.13013.

Adjuvant continuous metronomic adriamycin +cyclophosphamide followed by weekly nab-paclitaxel for high- risk early stage breast cancer

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Abstract

Purpose: Many studies have sought to optimize the dosing schedule of adjuvant chemotherapy in early stage breast cancer. Here we assessed the use of continuous metronomic weekly doxorubicin plus daily oral cyclophosphamide (AC) with continuous G-CSF growth factor support for 12 weeks followed by weekly nab-paclitaxel (nP) for 12 weeks.

Method: A non-randomized phase II clinical trial was designed to assess (1) DFS at 2 years, (2) dose delivered, (3) use of nP in the adjuvant setting, and (4) toxicities. The dosing of A was 24mg/m² IV weekly and C was 60mg/m² oral daily (with scheduled filgrastim 5mcg/kg 6days/week); nP, 100mg/m² IV weekly. For patients with HER2+ disease, trastuzumab was started during the nP portion of therapy and continued for 12 months.

Results: Sixty patients enrolled with a median follow-up of 6 years. 58% had node positive disease. Receptor categories included hormone receptor positive/ HER2 negative (n=25; 42%); triple negative (n=19; 32%); or HER2 positive (n=16; 27%). DFS at 2 years was 93%. Mean dose delivered was greater than 90% for metronomic AC and 88% for nP. Treatment was well-tolerated with a 2% incidence of febrile neutropenia.

Conclusions: Continuous metronomic AC followed by nP was well tolerated in our patients with comparable DFS to historical controls.

Keywords

Adjuvant chemotherapy; nab-paclitaxel; metronomic

Introduction

Cytotoxic chemotherapy given after surgery for breast cancer results in fewer recurrences in patients at high risk on the basis of biology or stage [1]. Chemotherapy regimens have evolved to increase intensity and density, both of which are maximized with better supportive care such as anti-emetics and granulocyte growth factors [2]. During the prior decade, a generally accepted standard of care option for high-risk early stage patients was the regimen of every 2 week dose dense doxorubicin plus cyclophosphamide for 4 cycles followed by paclitaxel delivered either every 2 weeks for 4 cycles or weekly for 12 cycles (ddAC x4 -> ddT x4 or wT x12).

In this report, we present data from a non-randomized phase II clinical trial demonstrating tolerability and feasibility of continuous metronomic doxorubicin plus daily oral cyclophosphamide (AC) for 12 weeks with continuous G-CSF growth factor support followed by nab-paclitaxel (nP) for 12 weeks for high-risk early stage breast cancer. This regimen represents an intended 20% greater intensity for doxorubicin and 40% for cyclophosphamide. nP is formulated to deliver drug without toxic carrier molecules and can be safely administered at higher doses than generally tolerated with conventional paclitaxel. The minimum dose intensity increase for the taxane in the current protocol compared to standard of care weekly dosing is 25%. We hypothesized that the regimen under study would compare favorably to standard of care from the prior decade in terms of toxicity profile, DFS, and OS for early stage breast cancer.

Patients and Methods

Study Design and Treatment:

This single-arm phase II study included women who met one of the following criteria 1) 4 positive nodes, 2) 1–3 positive nodes with either ER- or HER2+ disease, or 3) high risk node negative disease that was either HER2+ or ≥ 2.0 cm primary tumor. Patients on the study were treated with AC (doxorubicin 24 mg/m²/wk given intravenously each week and cyclophosphamide 60 mg/m²/d given orally each day) with filgrastim (G-CSF) self-administration (5 mcg/kg) on all days except infusion days for 12 weeks followed by weekly nP (100 mg/m²) for 12 weeks. No primary prophylaxis with G-CSF was mandated during nP. Concurrent trastuzumab was started at the time of nP for patients with HER2+ disease and continued for 12 months. Chemotherapy was completed before radiation therapy (XRT) when XRT was indicated and prior to initiation of endocrine therapy with either tamoxifen or an aromatase inhibitor in all patients with hormone receptor positive disease.

Patient population

Women with histologically confirmed breast carcinoma that had been surgically resected were eligible. HER2, ER, and PR were reported by using local institutional standards. Patients could not have received prior chemotherapy, hormonal, or radiation therapy for breast cancer. Patients had to have adequate hematologic, renal, and hepatic function, and a Zubrod performance status of 0 to 2. Patients with clinically apparent cardiac disease were not eligible. Patients ≥ 60 years of age or with a history of hypertension were required to

have evaluation of their ejection fraction prior to enrollment. Patients with HER2+ disease with a treatment plan including trastuzumab were required to have evaluation of ejection fraction prior to enrollment. The ejection fraction had to be within the institutional normal range for enrollment.

Assessments and Toxicity Management

Validation of inclusion and exclusion criteria and a medical history were completed at baseline. Toxicity was assessed at each patient visit and for 30 days after the last dose. Follow up was done every 3 months for 2 years, every 6 months for 2 years, and then annually. Lab work, imaging studies (as indicated) and assessments of health status occurred at these visits.

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (version 3). AC was held for absolute neutrophil count less than 1,500 and/or platelet count less than 100,000. For neutropenia associated with AC, 25% dose reduction of both agents was initiated and continued through all subsequent cycles. nP was held for absolute neutrophil count less than 1,000 and/or platelet count less than 75,000. For patients with fever >38 degrees with ANC <500, persistent neutropenia <500 for >1 week, or delay of next treatment due to persistent neutropenia, G-CSF was initiated with nP. If neutropenia reoccurred despite G-CSF, nP dose was reduced to the -1 dose level (80mg/m²). For other Grade 3 or 4 toxicities such as thrombocytopenia and peripheral neuropathy, nP was held and reduced at the next infusion to the -1 or -2 (65mg/m²) dose level depending on the specific toxicity.

Statistical Methodology and Analysis

The target enrollment was 60 patients to allow for drop out and assure 50 evaluable patients. The primary objective was DFS at 2 years compared to historical controls. The DFS at 2 years for dose dense AC followed by paclitaxel is approximately 0.85. If at least 42 of 50 patients are alive and disease-free at 2 years (observed rate of 0.84), then we were at least 90% confident that the true rate exceeded 0.75.

Delivered total dose of each drug was calculated for each patient. DFS was measured from the date of first dose until the date of any relapse of breast cancer (local or distant), a new breast cancer or other type of cancer, death as a result of any cause without relapse of breast cancer, or last patient contact. OS was measured from the date of first dose to the date of death or to the date of last contact. DFS and OS were assessed using the Kaplan-Meier method. The analysis was conducted on the intent-to-treat population, which included all enrolled patients, and the safety analysis included all patients who received at least one dose of study drug.

Results

Between June 2006 and April 2009, 60 women with operable stage I to III invasive breast cancer were registered in the study. Median age was 50 (range 30–69). 58% of patients had node positive disease, 27% had her2+ disease, and 32% had triple negative disease. Table 1 shows baseline demographic characteristics. Of 60 registered patients, all 60 received AC

but 4 patients received no nP due to early study discontinuation during the AC portion. Median follow-up was 6 years.

34 patients (57%) completed 12 weeks of AC and 12 weeks of nP. For all patients, the percent of planned doses administered of doxorubicin was 92.6% and cyclophosphamide was 92.1%. The percent of planned doses administered of nP was 88.2% based on intent-to-treat and 92.9% when including only patients who still remained on study through at least one dose of nP. Of the 16 patients with HER2 positive disease, 15 patients remained on study through the nP portion and received trastuzumab as part of the study.

All women with estrogen receptor positive and/or progesterone receptor positive disease were offered adjuvant endocrine therapy (Table 2). One patient declined.

Of the 60 patients, 7 died. 1 patient was found to have metastatic (CNS) disease after 11 weeks of AC and was removed from the study. The median follow up for living patients was 6 years, and during that period of time, there were 7 recurrences of breast cancer (2 local and 5 distant). Of the 7 patients who had a recurrence, 5 had stage III disease at time of diagnosis and 2 had stage II disease. Four patients had ER/PR+ Her2- disease, two patients had triple negative disease, and 1 patient had ER/PR+ Her2+ ("triple positive") disease. Non-recurrence DFS events included contralateral breast cancer (1), squamous cell carcinoma of unknown primary (1), and papillary thyroid cancer (1).

Kaplan Meier (KM) curves and estimates were performed to show the OS and DFS, overall and by subgroups: (a) ER + and/or PR +, HER2-, (b) Her2+ patients, (c) triple negative (Figure 1 and Table 4). No statistically significant differences were observed between subgroups ($p=0.172$ for OS and $p=0.715$ for DFS, respectively).

The most common grade 3–4 adverse events were neutropenia, mucositis, hand-foot syndrome, and neuropathy (Table 5). On the basis of clinical judgment, filgrastim was used in 37 patients (66.1%) during the nP portion. Dose holds or reductions for any reason were needed in 43 (71.7%) patients. No patients died from treatment-related causes. Five patients required hospitalization or emergency room evaluation during the course of therapy: hemorrhoidal bleed (1), pneumonia (1), neutropenic fever (1), musculoskeletal pain (1), and motor vehicle accident (1). Of the 15 patients receiving trastuzumab, 2 patients (13.3%) had a decrease in LVEF to less than 50%. Three patients (20%) had a decrease of 10% in LVEF at some point in the study. No patients developed symptomatic congestive heart failure.

Discussion

The addition of taxanes and optimization of the dosing schedule of anthracycline-based chemotherapy has improved outcomes in women with high-risk early-stage breast cancer [2–4]. Based on the reported efficacy of weekly paclitaxel [5, 6] and the benefit of nP seen in patients with metastatic breast cancer [7], we elected to study nP in sequential combination with metronomic AC.

Although there were early signals of improved efficacy of more continuous dosing [8], recent reporting of SWOG S0221 favored every 2-week dosing over continuous metronomic

AC as used in our study [4]. This trial featured a randomization to 4 arms of treatment in a 2 × 2 design evaluating dose density with every week versus every 2-week therapy for both the AC component (15 or 12 weeks of therapy) and the paclitaxel component (12 weeks regardless of schedule). The continuous schedule arm was closed early since statistical analysis showed the futility of continuing this arm; hazard ratio was 1.21 after the first interim analysis after enrollment of 2716 patients. DFS at 5 years was 81% overall and a log-rank test comparing all four arms simultaneously was not significant for the primary outcome ($p=.11$). However, a Cox model comparing every 2-week AC with every 2-week paclitaxel to continuous dosing AC with every 2-week paclitaxel yielded a hazard ratio of 1.32 ($p=0.22$) in favor of the every 2-week dosing schedule. Toxicities were different between the two arms with more stomatitis and dermatologic toxicities in the continuous AC arm and more myelosuppression in the every-2-week arm. A statistically significantly lower number of patients in the continuous treatment arm completed all treatments (83% vs 88%, $p<0.001$). Authors concluded that treatment selection should be based on toxicity, cost, or patient preference since DFS was equivalent in all arms. However, based on toxicity profile, they did not recommend routine use of the continuous AC regimen. In an unplanned subset analysis, there was a benefit in terms of overall survival for the group with triple negative breast cancer seen with the every 2-week regimen. Interestingly, there was no benefit seen for DFS.

Our study showed excellent DFS of 93% at 2 years, which is very comparable to prior studies evaluating anthracycline followed by taxane sequencing [5]. At 6 years of follow up, the DFS and OS are 82% and 88%, respectively. However, our small sample size limits ability to extrapolate these results to different subtypes and stage. In addition, some of the benefit seen in HER2+ patients may be attributable to trastuzumab therapy.

This regimen of continuous metronomic doxorubicin with daily oral cyclophosphamide followed by weekly nP was well-tolerated in our patients with a positive signal for efficacy. However, based on the results of S0221, a larger, randomized study, continuous metronomic AC may not be advisable over every 2-week AC. The substitution of weekly nP for paclitaxel may be of benefit in patients with infusion reactions or have poor tolerance of steroids due to comorbidities such as diabetes.

Acknowledgements:

Funding: National Cancer Institute T32 CA009515 (EC); P30CA015704; Celgene Corporation (GE). Writing and submission assistance from Tabitha Headrick.

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Figure 1:
 “OS and DFS for entire cohort and by tumor type subgroup [Color figure can be viewed at wileyonlinelibrary.com]”

Table 1:

Patient and tumor characteristics at baseline

	Patients (N=60)
Age (years)	50 (29–69)
Stage at diagnosis	
I	7 (11.7%)
II	32 (53.3%)
III	21 (35.0%)
Positive nodes	
None	25 (41.7%)
1–3	18 (30%)
4	17 (28.3%)
Tumor size (cm)	
<0.5	0
0.5–1.0	2 (3.3%)
1.1–2.0	19 (31.7%)
2.1–5.0	27 (45%)
>5.0	12 (20%)
Histology	
Infiltrating ductal	51 (85%)
Infiltrating lobular	6 (10%)
Other	3 (5%)
Estrogen receptor status	
Negative	27 (45%)
Positive	33 (55%)
Progesterone receptor status	
Negative	30 (50%)
Positive	30 (50%)
Her2 status	
Negative	44 (73.3%)
Positive	16(26.7%)
Subgroup	
ER+ or PR+, HER2-	25 (41.7%)
Any HR, HER2+	16 (26.7%)
Triple negative	19 (31.7%)
Menopausal state	
Premenopausal	29 (48.3%)
Postmenopausal	26 (43.3%)
Unknown	5 (8.3%)

Table 2:

Adjuvant endocrine therapy (N=33)

Tamoxifen	22 (66.7%)
Aromatase inhibitor	25 (75.8%)
Ovarian suppression (LHRH agonist)	6 (18.2%)
Oophorectomy	5 (15.2%)

Table 3:

Overall study population DFS and OS events

Event	No. of patients	%
Recurrence	8	13.3%
Local	2	25%
Distant	6	75%
Recurrence or second cancer	11	18.3%
Death, any cause	7	11.7 %
Death without relapse	1	1.7 %
Death on treatment	0	0 %

Table 4:

DFS and OS (2 and 6-year estimates)

	2 Year DFS	2 Year OS	6 Year DFS	6 Year OS
All patients	93%	98%	82%	88%
ER or PR+, HER2-	92%	100%	80%	80%
HER2+	100%	100%	88%	100%
Triple negative	89%	95%	79%	89%

Table 5:

Adverse Events

Adverse Event	Grade 3	Grade 4
Hematologic		
Anemia	3	0
Neutropenia	21	12
Thrombocytopenia	1	0
Leukopenia	3	0
Nonhematologic		
Nausea	3	0
Fatigue	2	0
Arthralgia	1	0
Neuropathy	4	0
Mucositis	7	0
Hand-foot	5	0
Hypokalemia	2	0
Hypocalcemia	0	1
Pulmonary embolism	0	1