

Feasibility of AC/EC Followed by Weekly Paclitaxel in Node-positive Breast Cancer in Japan

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Abstract. *The feasibility and efficacy of adriamycin or epirubicin in combination with cyclophosphamide followed by weekly paclitaxel (AC/EC-weekly PAC) as adjuvant chemotherapy for breast cancer was investigated. Patients and Methods: Node-positive breast cancer was treated with AC/ EC-weekly PAC, namely AC at 60/600 mg/m² or EC at 90/600 mg/m² ×4 at three-week intervals, followed by weekly PAC (80 mg/m²) ×12, namely four cycles of single weekly administration for three weeks followed by a one-week rest (3×4 PAC) or single weekly administration for 12 consecutive weeks (12 PAC). Results: One hundred and three of 109 consecutive patients enrolled were analyzed, of whom 96 (93.2%) completed the regimen. Grade 3/4 neutropenia occurred in 52.4% receiving AC/EC, and 10.9% of 55 receiving 12 PAC but only 2.1% of 48 receiving 3×4 PAC. Neuropathy disorders occurred in more than half receiving PAC, which did not improve after one-*

week rest in 3×4 PAC. Conclusion: AC/EC-weekly PAC is feasible and without serious complications.

Although anthracycline-based regimens are associated with a lower risk of recurrence and death in patients with breast cancer than those based on cyclophosphamide, methotrexate, and fluorouracil (CMF), outcomes remain unsatisfactory, particularly in patients with lymph node involvement (1). Various dose and schedule combinations as well as combinations with non-cross-resistant drugs have thus been investigated.

Among the latter, the addition of taxane appears to provide significant benefit, particularly in node-positive and hormone receptor-negative cases (2, 3). In addition, clinical trials suggest that low-dose weekly paclitaxel might be superior to higher doses given less frequently in both metastatic and adjuvant settings (4, 5). With regard to safety, paclitaxel administered weekly at the relatively low dose of 80 mg/m² appears well tolerated compared with administration once every three weeks, with a reduced risk of neutropenic fever and grade 2 or higher neuropathy (6). In addition, weekly administration at 80 mg/kg for three weeks followed by a one-week withdrawal period has been shown to be effective in the treatment of metastatic breast cancer (7).

Here, to investigate the efficacy of treatment in routine clinical practice, a multi-center feasibility study of a low-dose weekly paclitaxel regimen was conducted in patients with resected node-positive breast cancer.

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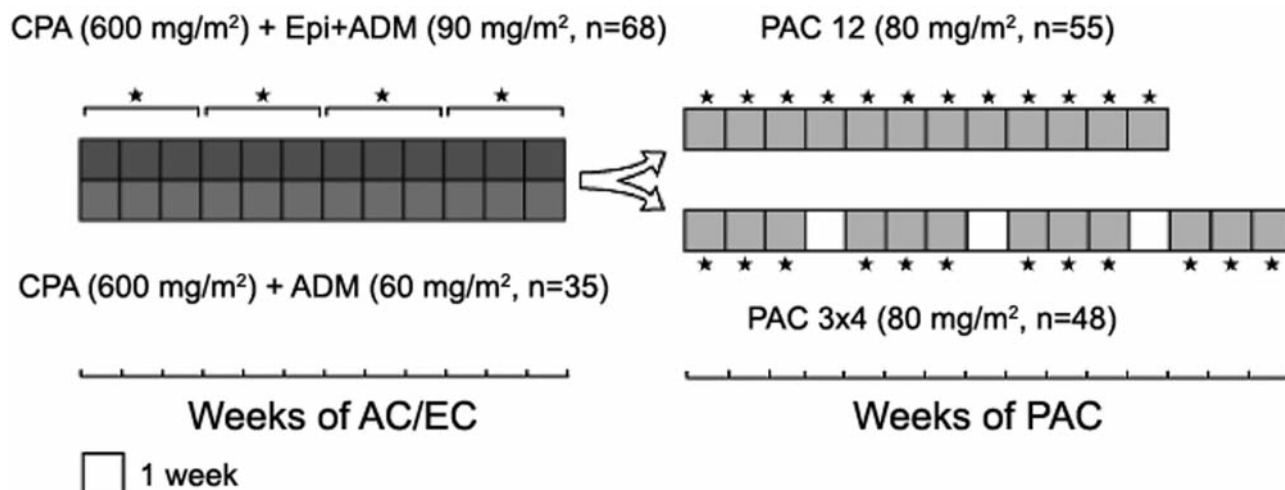


Figure 1. Schematic outline of the treatment protocol. AC at 60/600 mg/m² or EC at 90/600 mg/m² was given four times at three-week intervals, followed by weekly PAC (80 mg/m²) ×12, either as single weekly administration for 12 consecutive weeks (12 PAC) or four cycles of single weekly administration for three weeks followed by a one-week rest (3×4 PAC).

Patients and Methods

The study enrolled consecutive patients with completely resected breast cancer with positive lymph nodes from nine centers between May 2003 and January 2007. Enrollment criteria included an absolute neutrophil count $\geq 2,000/\mu\text{L}$ and platelet count $\geq 100,000/\mu\text{L}$, normal total bilirubin, aspartate aminotransferase and alanin aminotransferase (AST/ALT) ≤ 2.5 -fold the upper limit of normal, alkaline phosphatase (ALP) ≤ 4 -fold the upper limit of normal, normal carcinoembryonic antigen and cancer antigen 15–3, and no evidence of disease on computed tomography of the chest, abdomen and pelvis. Patients with a history of unstable angina, myocardial infarction, congestive heart failure, or other serious medical illness, as well as those unable to provide consent were excluded. Written informed consent was obtained from each patient. The study was reviewed and approved by the Institutional Review Board of Yokohama City University Medical Center.

Treatment plan. Four cycles of adriamycin (A) and cyclophosphamide (C) at doses of 60/600 mg/m² or epirubicin (E) and cyclophosphamide at 90/600 mg/m² once every three weeks, followed by paclitaxel (PAC) (80 mg/m²) given weekly for 12 weeks were planned (Figure 1). Selection of adriamycin or epirubicin was at the discretion of the attending physician. For weekly PAC administration, the drug was given by single weekly administration for 12 consecutive weeks (12 PAC) or in four cycles of three consecutive weekly administrations followed by a one-week rest each (3×4 PAC) as determined by the attending physician. Sub-analyses were performed to compare the 12 PAC and 3×4 PAC schedules. Pre-medication for AC or EC consisted of a 5-HT₃ serotonin receptor antagonist (*e.g.* granisetron 2 mg) orally and dexamethasone 20 mg intravenously. Pre-medication for PAC included oral or intravenous dexamethasone 10 mg or a steroid equivalent, diphenhydramine (50 mg, or another H1 blocker), and an H₂ blocker at approximately 30 minutes before PAC infusion. If

no hypersensitivity reaction was experienced after the first two doses of PAC, pre-medication could be altered at the discretion of the physician. Actual body weight was used for body surface area calculations. A complete blood count with leukocyte differential was performed before each chemotherapy treatment. Patients were seen every two to three weeks during treatment for history and physical examination and assessment of performance status and toxicity.

Dose modifications. In patients experiencing neutropenic fever (absolute neutrophil count $< 1,000/\mu\text{L}$ and body temperature $\geq 38.5^\circ\text{C}$) or grade 3 or 4 non-hematologic toxicity, day 1 doses in the subsequent cycles were reduced, but doses in the current cycle were administered according to the protocol. A maximum of two dose reductions was allowed. When platelet count $< 100,000/\mu\text{L}$, absolute neutrophil count $< 1,500/\mu\text{L}$, or failure of non-hematologic toxicities (excluding nausea, emesis, appetite loss and alopecia) to recover to \leq grade 1 were noted, either singly or in combination, on the scheduled start day of the subsequent cycle, treatment was delayed by up to one week, and complete blood count and toxicity grading were repeated weekly. Prophylactic G-CSF was not used. Patients requiring a treatment delay of more than three weeks were removed from the study.

Radiotherapy. Radiotherapy in patients treated with breast conservation was conducted according to standard institutional dosing guidelines and techniques.

Hormonal therapy. Patients whose tumors were either estrogen or progesterone receptor-positive were offered either an LH-RH analogue for 2 years after chemotherapy or tamoxifen for 5 years, or both. Postmenopausal patients were offered anastrozole as an alternative to tamoxifen.

Follow-up. To estimate outcomes and monitor long-term toxicities, patients were followed closely by history and physical examination at 4-month intervals for years 1–3, 6-month intervals for years 4–5,

Table I. Patient characteristics.

	Pac 12 (N=55)	Pac 3x4 (N=48)	All Patients (N=103)
Median age (range)	53 (35-71)	55 (37-75)	54 (35-75)
PS			
0	55	48	103
1	0	0	0
Stage			
IIA	16	15	31
IIB	32	24	56
IIIA	6	6	12
IIIB	0	3	3
IIIC	1	0	1
HR			
ER+ or PgR+	44	34	78
ER- and PgR-	11	14	25
HER2			
3+	9	18	27
2+	12	5	17
1+	21	23	44
0	13	2	15
Nodes			
1-3	36	33	69
4-9	14	11	25
10+	5	4	9
RT			
Yes	31	31	62
No	24	17	41
Pathology			
ductal	50	47	97
lobular	3	1	4
other	2	0	2

Table II. AC/EC-related hematologic toxicity.

(n=103)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3 or 4 (%)
Febrile neutropenia			6		5.8
Leukocytopenia	6	11	18	52	68.0
Neutropenia	17	25	45	9	52.4
Thrombocytopenia	3		1		1.0
Anemia	38	13	2		2.0

Table III. PAC-related hematologic toxicity.

PAC 12 (n=55)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3 or 4 (%)
Leukocytopenia	10	8	3	1	7.3
Neutropenia	23	17	6		10.9
Thrombocytopenia					
Anemia	23	13			
Febrile neutropenia					
PAC 3x4 (n=48)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3 or 4 (%)
Leukocytopenia	11	3	1		2.1
Neutropenia	15	13	1		2.1
Thrombocytopenia		1			
Anemia	19	8			
Febrile neutropenia					

and annually after year 5. Each visit included a complete blood count, liver function tests, and measurement of carcinoembryonic antigen and cancer antigen 15-3. Computed tomography scan of the chest, abdomen, and pelvis and a bone scan (or both) were considered if clinically indicated by symptomatology or abnormal laboratory values at the discretion of the physician. Mammography was performed on the remaining breast(s) annually.

Statistical analysis. In general, adjuvant chemotherapy is successfully completed in approximately 80% of cases. For the present study, when the expected completion rate was set at 90%, 100 cases were required to prove feasibility with an overall two-sided significance of $p < 0.05$. Based on this calculation, it was planned to accrue a total of 100 patients.

Results

Patient characteristics. A total of 109 patients were enrolled in the study between May 2003 and January 2007. Six inappropriate cases were excluded (2 node-negative and 4 metastatic disease), leaving a final study population of 103

patients. Median age was 54 years (range, 35-75 years), and the mean number of positive nodes was 4.2 (range, 1-36). Clinical stage at diagnosis was categorized according to the tumor-node metastasis classification (8). Pathological subtypes of breast cancer by regimen are shown in Table I.

Treatment. By regimen, 35 of the 103 analyzed patients were treated by AC and 68 by EC. For PAC, 55 received 12 PAC and 48 received 3x4 PAC. A total of 96 of 103 patients (93.2%) completed the full treatment plan. Treatment was stopped prematurely in seven patients (1 with AC/EC and 6 with weekly PAC, 5 with 12 PAC, 1 with 3x4 PAC), due to hematologic toxicity of febrile neutropenia during EC (n=1); allergy to alcohol (n=2), hypotension (n=1) and nasal bleeding (n=1) during 12 PAC, and dysgeusia and mouth dryness (n=1) during 3x4 PAC. AC and EC doses were decreased to level 1 in three cases, whereas no decreases occurred in treatment with 12 PAC and 3x4 PAC. Actual and relative dose-intensities of adriamycin, epirubicin and

Table IV. AC/EC-related non-hematologic toxicity.

(n=103)	Grade 1	Grade 2	Grade 3	Grade 4
Alopecia	4	99		
Nausea	34	12	1	
Appetite loss	7	2		
Change in taste	11	3		
Fatigue	21	3	1	
Constipation	2	23		
Diarrhea	1	1		
Thirst		2		
Stomatitis	12	1	1	
Cystitis	1			
Cough	1	1		
Nail discoloration	3			
Menstrual disorder		1		
Tonsillitis	1			
Depression		2	1	
Insomnia		1		
Sweating	1			
Hypersensitivity	1			
Muscle pain	1	1		
Vessel pain	1	1		

Table V. PAC-related non-hematologic toxicity.

	PAC 12 (n=55)			PAC 3x4 (n=48)	
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2
Neuropathy	25	4	1	17	9
Arthralgia/Myalgia	6	1		1	1
Appetite loss	1			1	
Nausea	3	2			
Dysgeusia	10			3	1
Fatigue	12	2		8	
Constipation	2				7
Diarrhea	1			1	
Stomatitis	6	1		2	
Vessel pain	2				
Edema	1				
Hypersensitive	5	2		1	
Nail discoloration	2				
Nasal bleeding	2				
Fever	3			3	
Hypotension	1				
Depression				1	1

paclitaxel were 19.7 mg/m²/week and 98.4% in AC, 29.4 mg/m²/week and 98.0% in EC, 71.8 mg/m²/week and 89.7% in 12 PAC, and 63.1 mg/m²/week and 98.5% in 3x4 PAC, respectively. Completion rates for 12 PAC and 3x4 PAC were 90.9% and 97.9% , respectively. Treatment was stopped prematurely in 6 patients, 5 with 12 PAC and 1 with 3x4 PAC. No decrease in dose was required with weekly PAC treatment.

Treatment delays. With regard to AC/EC, treatment delays as defined by the protocol occurred in 14 of 411 (0.03%) cycles in 9 of 103 (7.8%) patients. The cause of delay was febrile neutropenia in 1 patient, grade 4 neutropenia in 5, pneumonia in 1, and patient discretion in 2.

For weekly PAC, delays with 12 PAC occurred in 74 of 660 (11.2%) cycles in 16 of 55 (29.1%) patients, and with 3x4 PAC in 10 of 576 (1.7%) cycles in 3 of 48 (6.3%) patients. The cause of delay with 12 PAC was grade 3 neutropenia in 3 patients, fatigue in 1, liver dysfunction in 1, cold in 3, cold and epistaxis in 1, diarrhea in 1, and patient discretion in 5 of 15 patients; and liver dysfunction in 1 and neuropathy in 2 of 3 patients with 3x4 PAC.

Hematologic toxicity. Hematologic toxicities are summarized in Tables II and III. During AC/EC, 70 of 103 (68.0%) patients developed grade 3/4 granulocytopenia (Table II), as did 4 of 55 (7.8%) receiving 12 PAC and 1 of 48 (2.1%) receiving 3x4 PAC (Table III).

Non-hematologic toxicity. During AC/EC, grade 2 alopecia occurred in all patients. Grade 3 toxicities occurred in four patients, with one case each of nausea, fatigue, stomatitis and depression. In contrast, no grade 4 non-hematologic toxicities were noted (Table IV). During weekly PAC, in contrast, sensory neuropathy was a common adverse event; although severe symptoms of grade 3 occurred in only 1 patient with 12 PAC, grade 1/2 neuropathy occurred in 29 of 55 (52.7%) patients receiving 12 PAC and in 26 of 48 (54.1%) receiving 3x4 PAC (Table V).

Discussion

In this feasibility study in patients with resected node-positive breast cancer, it was found that a regimen of AC/EC followed by weekly PAC was well tolerated, with low hematologic toxicity and easily controlled nausea. This safety profile warrants additional investigation of this therapy, notwithstanding that neurotoxicity is a major concern in PAC-associated treatment. Follow-up of patients in this study will demonstrate results for the efficacy of this treatment, which is a secondary endpoint of disease-free and overall survival.

A large number of adjuvant taxane studies have been reported. The CALGB 9344 and NSABP B-28 trials demonstrated that AC plus PAC is superior to four cycles of AC alone, which in turn has equivalent efficacy to six cycles of CMF (9, 10). Many clinical studies have also

revealed that six or more cycles of 3- or 4-drug anthracycline-containing regimens are superior to six cycles of CMF (1).

To date, however, no evidence has been available to show which is more efficient, AC/EC-PAC or the “best” anthracycline-containing regimen without taxane. While efficacy in the French FEC 100 and Canadian CEF studies was satisfactory, concerns were raised by their high frequency of neutropenia (11, 12).

Delays and reductions in chemotherapy dosing appear to have a significant negative impact on overall survival in breast cancer patients treated with adjuvant anthracycline-based regimens (13, 14). In Hryniuk *et al.*'s study, for example, patients exposed to a delay of three or more cycles, or 15 or more days across the whole regimen, or less than 95% of relative dose intensity, showed significantly worse 10-year overall survival than those with no dose delay or reduction (13). In the French Adjuvant Study Group 05 with the FEC100 regimen (11), the relative dose intensity of 86.1% was considerably lower than the 95% mentioned above, suggesting that the administration of this regimen without dose delays and reductions may be difficult. In the present study, in contrast, relative dose intensity of AC/EC-PAC was 98.4% , 98.0% , 89.7% , and 98.5% for AC, EC, 12 PAC, and 3×4 PAC, respectively, all of which were much better than that with FEC100.

Of interest, the relative dose intensity of 12 PAC, at 89.7% , was lowest of the four phases of this regimen. Overall, 7 of 103 patients did not complete the full course of treatment, most of whom (5/7) were in the 12 PAC phase. Moreover, treatment delays occurred more frequently in this phase, at 29.1% compared with 6.3% in 3×4 PAC. This higher acceptability of 3×4 PAC than 12 PAC was due to a lower incidence of hematologic toxicity. Nevertheless, dose intensity remained higher with 12 PAC than 3×4 PAC, at 71.9 vs. 63.1 mg/m²/week. Given the strong significance of dose intensification to the efficacy of adjuvant chemotherapy, these findings may suggest the suitability of 12 PAC for adjuvant use (5).

Among other important findings, a high incidence of neurosensory disorders after repetitive cycles of weekly PAC were also noted, albeit with insufficient severity to cause withdrawal from the study. This adverse effect was the major problem with long-term treatment with PAC and caused substantial patient discomfort, resulting from its frequently long-term duration. Interestingly, no differences in non-hematologic toxicities between 12 PAC and 3×4 PAC were observed, including neurosensory disorders: whereas one week of PAC cessation lessened the hematologic toxicity, it did not improve toxicity for peripheral neurosensory systems. Identification of a safe and effective neuroprotective agent that does not reduce cell cytotoxicity would significantly enhance patient quality of life during treatment.

Recently, Sparano reported a randomized trial of AC followed by one of four taxane-based treatments, namely paclitaxel administered weekly or every 3 weeks, or docetaxel administered weekly or every 3 weeks. Results showed that 5-year overall survival was highest with weekly paclitaxel. Taking these and the present findings together, it is considered that AC/EC followed by weekly PAC is the most effective regimen for adjuvant treatment of breast cancer (5).

In summary, this study showed that AC/EC followed by weekly PAC was well-tolerated with low hematologic toxicity and easily controlled nausea. The safety profile of this therapy warrants additional investigation, particularly with regard to neurotoxicity, the major concern of PAC-associated treatment. No difference in the occurrence rate of peripheral nervous system disorder was observed between PAC by 12 consecutive weekly doses and by 3 weekly doses followed by a 1-week pause. Patients should be followed further to determine the secondary end-points of this study, namely disease-free survival and overall survival.

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