Does Timing of Adjuvant Chemotherapy for Early Breast Cancer Influence Survival?

By C. Shannon, S. Ashley, and I.E. Smith

Purpose: **Theoretically, patients with early breast cancer might benefit from starting adjuvant chemotherapy soon after surgery, and this would have important clinical implications. We have addressed this question from a large, single-center database in which the majority of patients received anthracyclines.**

Patients and Methods: **A total of 1,161 patients from a prospectively maintained database treated with adjuvant chemotherapy for early breast cancer at the Royal Marsden Hospital (London, United Kingdom), including 686 (59%) receiving anthracyclines, were retrospectively analyzed. The disease-free survival (DFS) and overall survival (OS) of the 368 patients starting chemotherapy within 21 days of surgery (group A) were compared with those of the 793 patients commencing chemotherapy ≥ 21 days after surgery (group B). Median follow-up time was 39 months (range, 12 to 147 months).**

Results: **No significant difference in 5-year DFS was found between the two groups overall (70% for group A *v* 72% for group B; *P* = .4) or in any subgroup. Likewise, there was no difference in 5-year OS (82% for group A *v* 84% for group B; *P* = .2) or when the interval to the start of chemotherapy was considered as a continuous variable (*P* = .4).**

Conclusion: **We have been unable to identify any significant survival benefit from starting adjuvant chemotherapy early after surgery, either overall or in any subset of patients.**

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THE SURVIVAL benefit of adjuvant chemotherapy for operable breast cancer is now firmly established,[1] but its optimal timing after surgery remains uncertain. Adjuvant chemotherapy normally starts within a few weeks of surgery, but it is unclear whether there is any gain from starting as soon as possible or whether a delay has an adverse outcome.

There are theoretical reasons to believe that starting chemotherapy early might improve survival. First, in animal models, a phase of accelerated growth of micrometastases after the removal of the primary tumor has been demonstrated,[2,3] along with serum-transmissible growth factors responsible for accelerated growth of tumor at distant sites.[3,4] The administration of chemotherapy or endocrine therapy preoperatively or in the perioperative period prevented this accelerated growth.[5,6] Second, a delay in the initiation of systemic therapy theoretically increases the probability of the emergence of drug-resistant micrometastatic disease.[7] Third, there is evidence in animal models that the removal of the primary tumor leads to an increase in angiogenesis in the vascular bed surrounding metastases,[8] and it is postulated that one of the mechanisms of action of chemotherapy may be the inhibition of neoangiogenesis.

Two small clinical studies have suggested that patients who received chemotherapy within 28 to 35 days of surgery had improved disease-free survival (DFS) compared with those who received chemotherapy later.[9,10] More recently, a larger study analyzed the effect of timing of cyclophosphamide, methotrexate, and fluorouracil (CMF) chemotherapy on survival in premenopausal patients participating in the International Breast Cancer Study Group (IBCSG) trials I, II, and VI.[11] This study found a significant and clinically striking improvement in 10-year DFS in a small subset of premenopausal patients with estrogen receptor (ER)–absent tumors who started chemotherapy within 21 days of surgery compared with those commencing chemotherapy 21 days or more following surgery (60% *v* 34%; *P* = .0003). No similar benefit was seen for other patients (the majority).

In the current era of anthracycline-based adjuvant chemotherapy, we wished to investigate further whether there was a group of patients for whom it was particularly important to start treatment within the first 3 weeks after surgery. We have therefore reviewed a single-center database of more than 1,000 patients, the majority of whom were treated with anthracycline-based adjuvant chemotherapy.

PATIENTS AND METHODS

We identified retrospectively from a prospectively maintained database 1,161 patients treated with adjuvant chemotherapy for early breast carcinoma between January 1990 and June 2001 at the Royal Marsden Hospital (London, United Kingdom), either within clinical trials or on the basis of standard service guidelines. Six hundred eighty-six of these patients received anthracycline-based chemotherapy using combinations that mainly included epirubicin 60 mg/m^2 every 3 weeks for six courses (636 patients) or sometimes doxorubicin 60 mg/m^2 every 3 weeks for six courses (50 patients); the remaining 475 patients received CMF or mitoxantrone and methotrexate (MM). Data were collected on known prognostic factors including age, tumor size, grade, nodal status, number of involved lymph nodes, lymphovascular invasion, and hormone receptor status. The time from

From the Breast Unit, Royal Marsden Hospital; and the Institute of Cancer Research, London, United Kingdom.

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Address reprint requests to Ian E. Smith, MD, Royal Marsden Hospital, Fulham Rd, London SW3 6JJ, United Kingdom; e-mail: ian.smith@rmh.nthames.nhs.uk.

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surgery until the day of administration of the first cycle of adjuvant chemotherapy was recorded. The date of surgery was taken as the date of the first surgical excision of the primary tumor, whether or not a diagnostic biopsy had preceded this date. Patients were divided into two groups with respect to the initiation of adjuvant chemotherapy: those who received the first dose of chemotherapy within 21 days of surgery (group A) and those whose chemotherapy started 21 days or more after surgery (group B). Data on radiotherapy and adjuvant endocrine therapy were also recorded. Data available up to July 31, 2002, were used for this analysis. Median follow-up time was 39 months (range, 12 to 147 months).

Eighty-four percent of patients also received adjuvant endocrine therapy, nearly always tamoxifen, given concurrently with the start of chemotherapy for 5 years or in a trial comparing 2 years with 5 years of treatment.

All ER assays were conducted by a laboratory that participated in the relevant UK National External Quality Assessment Scheme throughout this period. Until 1992, ER was measured by multiple-point ligand-binding and dextran-coated charcoal assay, with values obtained by Scatchard plot analysis. Between 1993 and December 1994, ER was measured using enzyme immunoassay kits (Abbott Diagnostics, Chicago, IL). In both of these assays, values of $\geq$ 10 fmol/mg protein were considered positive. From 1995 onward, we used an immunocytochemical assay using the 1D5 antibody (DakoCytomation, Glostrup, Denmark). Results were calculated by H score, in which the percentage of cells staining with intensities of 0, 1, 2, or 3 were counted in 10 high-powered fields and summed to give a score, which ranged from 0 to 300. Scores of $\geq$ 20 were considered positive; this cutoff was formally established as being equivalent to an enzyme immunoassay concentration of $\geq$ 10 fmol/mg protein.[12]

Statistical Analysis

Baseline differences in pathologic variables between groups A and B were assessed by means of the χ^2 test or Fisher's exact test for categorical variables and the Mann-Whitney nonparametric test for continuous variables. Treatment imbalances were assessed by the χ^2 test or Fisher's exact test.

DFS was defined as the date of first surgery (excluding diagnostic biopsy) to the date of first relapse at any site or to the appearance of a second primary breast cancer. Overall survival was measured from the date of first surgical treatment to death from any cause or to last follow-up visit. Local recurrence was defined as tumor arising in the treated breast, chest wall, or regional lymph nodes. Survival curves were calculated using the Kaplan-Meier method[13] and differences assessed by the log-rank statistic.[14] The Cox proportional hazards regression model was used to test for the independent

Table 1. Patient Characteristics

Characteristic	Commencement of Chemotherapy: Before 21 Days After Surgery No.	%	On or After 21 Days After Surgery No.	%	*P*
Total no. of patients	368		793		
Age, years					
Median	48		48		.2
Range	18-68		22-75		
Tumor size, cm					
Median	2.0 cm		2.0		.9
Range	0-11 cm		0-12		
Grade					
1	21	5.7	32	4.0	.3
2	140	38.0	336	42.4	
3	201	54.6	390	49.2	
Not known	6	1.6	35	4.4	
Lymphovascular invasion					
Yes	204	55.4	403	50.8	.1
No	113	30.7	278	35.1	
Not known	51	13.9	112	14.1	
Estrogen receptor					
Positive	188	51.1	480	60.5	.1
Negative	89	24.2	178	22.4	
Unknown	91	24.7	135	17.0	
Nodal status					
Positive	241	65.5	487	61.4	.1
Negative	101	27.4	256	32.3	
Unknown	26	7.1	50	6.3	
No. of involved nodes					
1-3	147	39.4	312	39.3	.1
4 or more	90	24.5	174	21.9	
Treatment					
Conservative surgery	306	83.2	605	76.3	.01
Mastectomy	62	16.8	188	23.7	
Chemotherapy					
Anthracycline*-based chemotherapy	205	55.7	481	60.7	.1
CMF or MM chemotherapy	163	44.3	312	39.3	
Adjuvant endocrine treatment	318	86.4	656	82.7	.1
Local radiotherapy	281	76.4	565	71.2	.08

Abbreviations: CMF, cyclophosphamide, methotrexate, and fluorouracil; MM, mitoxantrone and methotrexate.

*Doxorubicin or epirubicin 60 mg/m^2 every 3 weeks for six cycles.

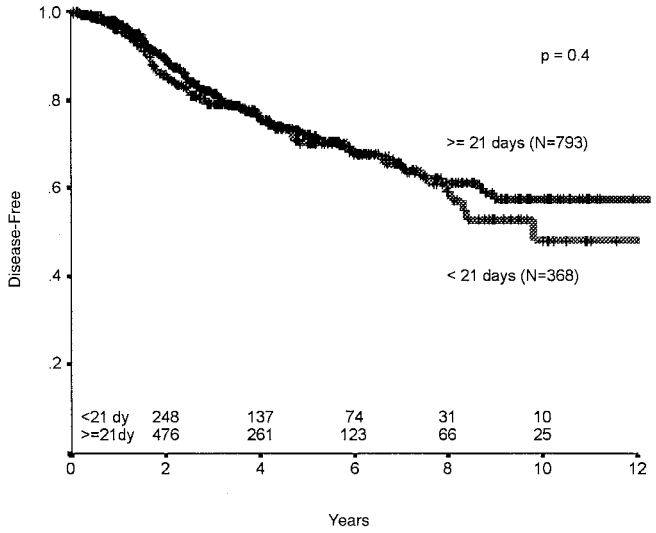

Fig 1. Kaplan-Meier curve for disease-free survival according to days from surgery to the start of adjuvant chemotherapy. dy, days.

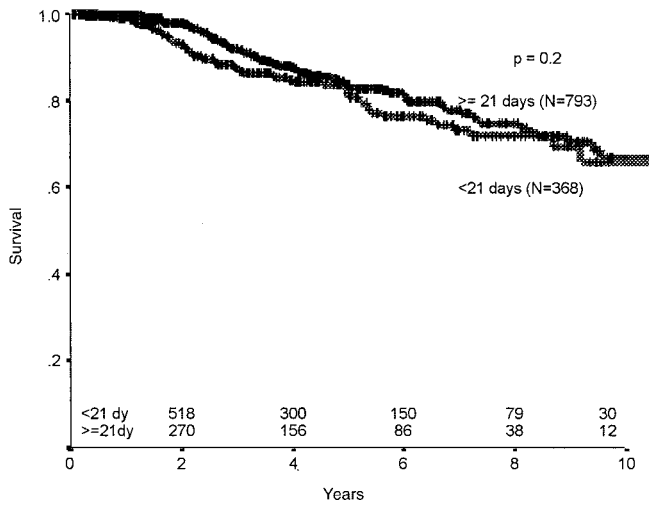

Fig 2. Kaplan-Meier curve for overall survival according to days from surgery to the start of adjuvant chemotherapy. dy, days.

effect of timing of chemotherapy after adjusting for other prognostic and treatment covariates.[15] Covariates considered in the regression models included pathologic tumor size, nodal status, grade, vascular invasion, ER status, type of chemotherapy, and adjuvant endocrine therapy use. All *P* values were two-sided.

RESULTS

Patient Characteristics

A total of 1,161 patients received adjuvant chemotherapy for early breast cancer between January 1990 and June 2001. Of these, 368 patients (31.7%) started chemotherapy within 21 days of surgery (group A), and 793 patients started chemotherapy 21 days or more after surgery (group B). Of the 368 patients in group A, 205 received anthracycline-based chemotherapy and 163 received either CMF or MM chemotherapy. Of the group B patients, 481 received anthracycline-based chemotherapy and 312 received CMF or MM chemotherapy.

Table 1 lists the patients' characteristics according to when their chemotherapy began. Patient characteristics are well balanced for age, tumor size, grade, incidence of lymphovascular invasion, nodal status, number of involved nodes, and ER status. The only significant difference between groups A and B is that group A patients were more likely to have had conservative breast surgery ($P = .01$).

DFS

There was no significant difference in DFS between patients starting adjuvant chemotherapy within 21 days of surgery and those commencing chemotherapy later (5-year DFS, 70% *v* 72%; $P = .4$; Fig 1). Likewise, there were no significant differences in DFS relating to age or ER status (Table 2). The Cox proportional hazards model was used to adjust the analysis for known prognostic factors of pathologic size, nodal status, number of involved nodes, grade, vascular invasion, ER status, type of chemotherapy, and use of adjuvant endocrine therapy. After adjusting for these factors, the effect of the surgery-chemotherapy interval remained nonsignificant ($P = .5$).

Overall Survival

There were no differences in overall survival between groups A and B (5-year survival, 82% *v* 84%, respectively; $P = .2$; Fig 2). After adjustment for known prognostic factors, there remained no difference in survival between the two groups ($P = .4$). We were likewise unable to show that the timing of

Table 2. DFS Analysis According to Days From Surgery to Start of Adjuvant Chemotherapy

	Commencement of Chemotherapy				
	Before 21 Days After Surgery		On or After 21 Days After Surgery		
Patients	n	5-Year DFS (%)	n	5-Year DFS (%)	*P*
Total No. of patients	368	70	793	72	.4
Age < 50 years	208	68	440	72	.3
ER negative	53	63	98	62	.6
ER positive	102	75	251	76	.6
Node positive	130	66	235	65	.9
Age ≥ 50 years	160	74	353	73	.9

Abbreviations: DFS, disease-free survival; ER, estrogen receptor.

Table 3. OS Analysis According to Days From Surgery to Start of Adjuvant Chemotherapy

Patients	Commencement of Chemotherapy: Before 21 Days After Surgery n	Before 21 Days After Surgery 5-Year OS, %	On or After 21 Days After Surgery n	On or After 21 Days After Surgery 5-Year OS, %	*P*
Total No. of patients	368	82	793	84	.2
Age < 50 years	208	83	440	85	.3
ER negative	53	74	98	70	.9
ER positive	102	93	251	92	.6
Node positive	130	78	235	83	.4
Age ≥ 50 years	160	80	353	81	.3

Abbreviations: OS, overall survival; ER, estrogen receptor.

chemotherapy influenced survival significantly for subgroups related to age or ER status (Table 3).

Continuous Variable Assessment

We also assessed whether any other time interval might influence outcome. One-third of the total patient population had their adjuvant chemotherapy initiated within 21 days of surgery, but the majority (65%) started adjuvant chemotherapy between day 14 and 35 after surgery (Fig 3). We found no effect of timing of chemotherapy on survival when the interval is considered as a continuous variable ($P = .4$). Likewise, we found no survival difference using either a 28-day ($P = .1$) or 35-day cutoff ($P = .3$).

DISCUSSION

Despite the experimental data discussed above,[3,8] which indicate that starting adjuvant chemotherapy early might have a survival benefit in early breast cancer, we have been unable to demonstrate this clinically. In a patient population treated in a single center during a 10-year period, we found no difference in outcome relating to how soon chemotherapy was started after surgery, either overall or in any subgroup of that population. This was the case whether we used an arbitrary 21-day cutoff point or assessed time as a continuous variable.

The largest previous study to address this question retrospectively analyzed data from three IBCSG trials of adjuvant CMF chemotherapy given to premenopausal, node-positive patients.[11] In this analysis, there was heterogeneity in the duration and total dose of chemotherapy received. A remarkable improvement in 10-year DFS (60% *v* 34%) was found for a small subgroup of premenopausal patients with node-positive, ER-absent tumors receiving CMF chemotherapy (226 of 1,788 patients [13%]) within 21 days of surgery compared with those starting treatment later (hazard ratio [HR], 0.48; 95% CI, 0.33 to 0.72; $P = .0003$). This far exceeds anything achieved by any specific form of adjuvant therapy itself and would have important clinical implications for delivery of treatment if confirmed. No similar benefit was seen for any other subgroup of patients.

It should be noted that patients who had received adjuvant oophorectomy or other endocrine therapy were excluded from the IBCSG study, whereas 84% of our patients also received endocrine therapy (nearly always tamoxifen) given concurrently with chemotherapy. It is possible that this had a confounding

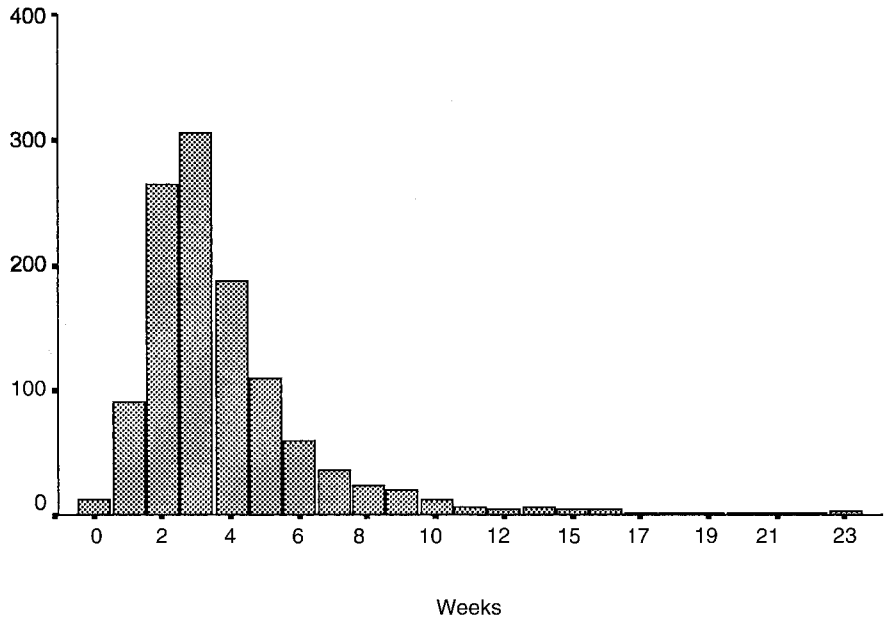

Fig 3. Interval from surgery to the start of adjuvant chemotherapy.

effect on the influence of chemotherapy. More importantly, although our finding of no benefit from early chemotherapy included premenopausal women with ER-negative cancers, we nevertheless cannot make direct comparisons on this issue between the IBCSG study and our own because of differences in ER categorization. Throughout the period of our study, ER was measured using a biochemical cutoff for positivity of $\geq$ 10 fmol/mg protein or an H score of $\geq$ 20, which was shown to equate to a biochemical cutoff of $\geq$ 10 fmol/mg protein[12] (see Patients and Methods). In contrast to the IBCSG but in common with most other centers, during the early 1990s, we did not create additional semiquantitative categories, including ER-absent and ER-low groups ($<$ 1 and 1 to 9 fmol/mg protein), respectively, for the ER-negative group. The IBCSG study did not report these two groups combined as a single ER-negative category. Nevertheless, it seems likely from their data that if they had done so, the significant effect noted in the ER-absent group would have been lost as a result of combination with the more numerous ER-low group of tumors in which no significant effect was seen. In this respect, therefore, our two studies appear to have consistent findings.

It should be noted, however, that diagnostic cutoffs for ER have changed in many centers such that what are now described as ER-negative tumors closely approximate the IBCSG description of ER-absent tumors. This is because of recent studies showing a better prognosis for tumors with as few as 1% cells staining positive when treated with tamoxifen.[16] Thus the small subgroup of ER-absent tumors is increasingly relevant to contemporary practice.

In other studies, Buzdar et al[17] likewise did not find any differences in DFS according to length of delay in initiation of chemotherapy. In their study of 462 patients receiving adjuvant fluorouracil, doxorubicin, and cyclophosphamide, overall 4-year DFS was 64%, 68%, 60%, and 63% for patient groups with delays of less than 10, 10 to 13, 14 to 17, or $\geq$ 18 weeks, respectively. In this study, only 13% of patients started chemotherapy within 10 weeks of surgery. This study therefore addressed the issue of long delays in the starting of adjuvant chemotherapy but provided less information on the significance of starting early in the postoperative period.

Pronzato et al[10] showed improved DFS for patients starting chemotherapy within 35 days of surgery. This study examined small numbers of patients (n = 229) receiving adjuvant intravenous CMF, and survival was analyzed according to the number of cycles received, dose-intensity, and time to start of chemotherapy. All three factors were significant in a univariate analysis, but only dose-intensity and time to start of chemotherapy retained independent prognostic significance in multivariate analysis. Brooks et al[9] also showed an improvement in DFS for patients with node-positive cancers receiving doxorubicin and cyclophosphamide chemotherapy within 4 weeks of surgery compared with those patients receiving delayed chemotherapy, but did not identify patient groups for whom the early chemotherapy was particularly important. In a retrospective Turkish study involving 1,167 patients receiving adjuvant chemotherapy between 1990 and 2000, it was found that time to start of adjuvant chemotherapy and time to progression were inversely related for patients receiving adjuvant chemotherapy within 4.8 months.[18] No data were given on what type of chemotherapy was used or whether there were specific subgroups who benefited from starting early. In their multivariate analysis, time to initiation of chemotherapy remained an independent prognostic variable. None of these studies provided sufficient numbers and/or demographic details to allow a premenopausal ER-absent subgroup equivalent to that identified by the IBCSG to be separately analyzed.

A trial of perioperative chemotherapy showed that patients receiving one course of perioperative polychemotherapy had significantly improved progression-free survival compared with patients having surgery alone, but not in patients who received additional conventional adjuvant chemotherapy subsequently.[19] In this study, the timing effect of one course of perioperative fluorouracil, doxorubicin, and cyclophosphamide was analyzed in the 1,198 patients who received prolonged adjuvant systemic treatment (chemotherapy or endocrine treatment). No effect of timing was found on overall survival (HR, 0.65; 95% CI, 0.78 to 1.17; $P = .65$) or progression-free survival (HR, 0.94; 95% CI, 0.80 to 1.12; $P = .50$). In addition, no effect of timing was found on locoregional control (HR, 0.88; 95% CI, 0.59 to 1.31; $P = .52$). This would suggest that total dose and duration of chemotherapy are more important than the timing of the start of chemotherapy. This trial suggests that one course of perioperative chemotherapy is better than no systemic therapy at all, but does not show that the perioperative timing confers a survival advantage superior to that of standard adjuvant therapy.

In conclusion, we have been unable to show any clinical benefit from commencing chemotherapy (usually anthracycline-based) early after surgery in any patient subgroup, including those we defined in the past as having ER-negative cancers. The issue remains unresolved, however, for the small subgroup with ER-absent tumors defined biochemically. Currently, this would approximate to immunohistochemically defined ER-negative tumors in an increasing number of centers, depending on cutoff. There are obvious practical and ethical difficulties in conducting a prospective randomized trial to address this issue, and the best way to proceed seems to be analysis of additional retrospective studies from large, prospectively assembled databases.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

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