Burdens and Benefits of Adjuvant Cyclophosphamide, Methotrexate, and Fluorouracil and Tamoxifen for Elderly Patients With Breast Cancer: The International Breast Cancer Study Group Trial VII

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Purpose: **Information on the tolerability and efficacy of adjuvant chemoendocrine therapy for older women is limited. We studied these issues using the data collected as part of the International Breast Cancer Study Group Trial VII.**

Patients and Methods: **Postmenopausal women with operable, node-positive breast cancer were randomized to receive either tamoxifen alone for 5 years (306 patients) or tamoxifen plus three consecutive cycles of classical cyclophosphamide (100 mg/m^2 orally days 1 to 14), methotrexate (40 mg/m^2 intravenous days 1 and 8), and fluorouracil (600 mg/m^2 intravenous days 1 and 8) every 28 days (CMF; 302 patients). The median follow-up was 8.0 years.**

Results: **Among the 299 patients who received at least one dose of CMF, women 65 years of age or older (n = 76) had higher grades of toxicity compared with women less than 65 years old (n = 223) (*P* = .004). More women in the older age group compared with the younger women experienced grade 3 toxicity of any type (17% *v* 7%, respectively), grade 3 hematologic toxicity (9% *v* 5%, respectively), and grade 3 mucosal toxicity (4% *v* 1%, respectively). Older patients also received less than their expected CMF dose compared with younger postmenopausal women (*P* = .0008). The subjective burdens of treatment, however, were similar for younger and older patients based on quality-of-life measures (performance status, coping, physical well-being, mood, and appetite). For older patients, the 5-year disease-free survival (DFS) rates were 63% for CMF plus tamoxifen and 61% for tamoxifen alone (hazards ratio [HR], 1.00; 95% confidence interval [CI], 0.65 to 1.52; *P* = .99). For younger patients, the corresponding 5-year DFS rates were 61% and 53% (HR, 0.70; 95% CI, 0.53 to 0.91; *P* = .008), but the test for heterogeneity of CMF effect according to age group was not statistically significant. The reduced effectiveness of CMF among older women could not be attributed to dose reductions according to dose received.**

Conclusion: **CMF tolerability and effectiveness were both reduced for older patients compared with younger postmenopausal node-positive breast cancer patients who received tamoxifen for 5 years. The development and evaluation of less toxic and more effective chemotherapy regimens are required for high-risk elderly patients.**

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PATIENT AGE PLAYS an important role in the epidemiology and management of breast cancer. Breast tumors are the most common cause of cancer death in women older than 65 years of age, and its incidence increases with age up to age 80, with a plateau between age 80 and 85 years.[1] In western countries, approximately 50% to 60% of all new cases are diagnosed in patients older than 65 years and as much as 40% in patients older than 70 years.

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Life expectancy has increased during the present century, and it has been calculated that a 65-year-old woman has 18.8 more years of expected life, a 75-year-old has 11.9 more years, and an 85-year-old has 6 more years of additional life. It seems particularly important, therefore, to give the best chance of cure even in older women.

Adjuvant hormonal treatment with tamoxifen has increased the cure rate of breast cancer both in node-positive and node-negative patients, as shown by the overview of all randomized trials.[2] Because hormone therapy is easier to administer and is associated with less toxic effects than chemotherapy, it is the logical first choice in adjuvant treatment, especially in the older group of patients. Between 1978 and 1981, the Ludwig Breast Cancer Study Group (predecessor of the International Breast Cancer Study Group [IBCSG]) conducted a randomized clinical trial in elderly patients (66 to 80 years of age) using 1 year of endocrine therapy with tamoxifen and low-dose prednisone versus no adjuvant treatment.[3] At a median follow-up of 16 years, this treatment significantly prolonged disease-free survival (DFS) and overall survival (OS), but most patients still died from cancer, confirming the need to improve therapeutic results. Giving tamoxifen for 5 years rather than for 1 year and adding chemotherapy to tamoxifen[4] were considered as possible approaches to achieve this objective.

Most clinical trials using adjuvant chemotherapy in breast cancer have set an age limit of 65 or 70 years for the accrual of patients. In the absence of such a limit, they have accrued only occasional elderly patients. (Current clinical trials of adjuvant therapy, however, rarely have upper age limits). The presence of frequently serious comorbid conditions[5] has generally limited the use of effective, intensive chemotherapy for these patients. In postmenopausal patients, the combination of chemotherapy (such as cyclophosphamide, methotrexate, fluorouracil [CMF] or CMF-like regimens) and tamoxifen gave conflicting results, with some studies demonstrating a significant advantage at least in terms of DFS.[6,7]

In 1986, the IBCSG initiated a randomized clinical trial (IBCSG Trial VII) to evaluate the effect of adding combination chemotherapy to 5 years of tamoxifen in postmenopausal women with node-positive operable breast cancer. There was no upper age limit, provided that patients were in good clinical performance status (PS), ie, an Eastern Cooperative Oncology Group (ECOG) PS $\leq$ 2. The aim was to study the role of three early courses of CMF added to tamoxifen and the value of three separate courses of CMF introduced later during treatment with tamoxifen. The results comparing treatment groups at the 5-year median follow-up have been published.[8] The present article evaluates the toxicity and tolerability of CMF among patients who received tamoxifen plus early CMF in the elderly population ($\geq$ 65 years old) compared with the younger postmenopausal women ($<$ 65 years old). The effectiveness of adding early CMF to tamoxifen compared with tamoxifen alone was also evaluated according to age group. The patient follow-up for the current report has been updated to a median of 8.0 years.

PATIENTS AND METHODS

Details of the entry criteria and of the trial in general have been described elsewhere.[8] Between July 1986 and April 1993, postmenopausal female patients with histologic evidence of axillary nodal involvement were accepted for entry. Postmenopausal status was defined as any of the following: (1) age greater than 52 years with $\geq$ 1 year amenorrhea; (2) age $\leq$ 52 years old with $\geq$ 3 years amenorrhea; (3) age $\geq$ 56 years with hysterectomy but no bilateral oophorectomy; or (4) biochemical evidence of cessation of ovarian function (for doubtful cases). Patients were enrolled after informed consent was conducted according to the guidelines established by local ethical review committees.

All patients had to have undergone mastectomy or a breast-conserving procedure and axillary node dissection within 6 weeks of randomization. Radiotherapy was mandatory in cases of breast-conserving surgery and had to be postponed until the end of the initial phase of chemotherapy. Tumor classification according to the International Union Against Cancer had to be T1-T2-T3pN1M0.

Proof of absence of metastases beyond the axilla by physical examination, chest x-ray, mammography of the contralateral breast, and bone scan were required before entry. The presence or absence of a comorbid condition was collected on the on-study form. Because the trial was not devoted to elderly women only, in 1986 we did not plan a formal measurement of comorbidity as is used in many geriatric trials today. Estrogen receptor (ER) analysis was also required at the time of entry. ER concentrations of $\geq$ 10 fmol/mg cytosol protein were considered positive and lower values negative. History of prior invasive malignancy, leukocyte count $<$ 4,000/μL, platelet count $<$ 100,000/μL, serum creatinine $>$ 1.5 mg/dL, bilirubin $>$ 1.5 mg/dL, and AST $>$ 40 IU/mL were additional conditions for ineligibility. Informed consent was required according to the local regulations of the participating centers.

The randomization was stratified according to ER status, type of surgery, and institution. Patients were randomized to one of four treatment groups: tamoxifen 20 mg/d for 5 consecutive years; tamoxifen plus three early consecutive courses of CMF (cyclophosphamide 100 mg/m^2 orally days 1 to 14, methotrexate 40 mg/m^2 intravenously days 1 and 8, and fluorouracil 600 mg/m^2 intravenously days 1 and 8; all repeated every 28 days) started on the same day as tamoxifen; tamoxifen plus three delayed courses of CMF on months 9, 12, and 15; or tamoxifen plus three early and three delayed courses of CMF. Dosages of CMF were modified for hematologic or mucosal toxicity.

Toxicity assessment followed a modified World Health Organization toxicity grading criteria (grade 3 level: WBC $<$ 1,000/μL, platelet count $<$ 50,000/μL, and neutrophil count $<$ 750/μL). Furthermore, toxicity grade was reported as 0 = none, 1 = mild, 2 = moderate, 3 = severe, and 4 = life threatening. To assess different kinds of toxicities, we grouped them as follows: hematologic (leukopenia, anemia, neutropenia, hemorrhage, infection, and thrombocytopenia); mucosal (stomatitis, diarrhea, gastritis, and cystitis); hepatic (hepatotoxicity); other (all other toxicities).

The protocol specified follow-up with physical examination and chemistries every 3 months for 2 years, then every 6 months until year 5, then yearly thereafter. Yearly mammography was mandatory. All study records were reviewed centrally by the data management and medical staff. Regular site-visit audits of the original medical records were conducted.

As part of the trial, quality-of-life (QOL) data were collected over time.[9,10] Patient-rated QOL was assessed using linear analog self-assessment scales for coping (Perceived Adjustment to Chronic Illness Scale [PACIS]. How much effort does it cost you to cope with your illness? none to a great deal), physical well-being (good to lousy), mood (happy to miserable), and appetite (good to none).[10] ECOG PS was assessed by the clinician. Baseline QOL was available for the self-reported measures but not for PS (except it had to be ≤ 2). All measures were assessed 2 months after the first day of adjuvant therapy and then every 3 months until 24 months. Data obtained up to 18 months are presented in this report.

Because the delayed chemotherapy treatment groups are not widely used today, we restricted the following analyses to the 302 eligible patients randomized to receive tamoxifen plus three courses of early CMF and the 306 eligible patients randomized to receive tamoxifen alone. To assess differences according to patient age at the time of randomization, we prospectively considered three groups before data analysis: less than 65 years old (436 patients), 65 to 69 years old (119 patients), and 70 years of age or older (53 patients). Because of the small number of patients in the oldest category, we combined the two oldest groups and present analyses comparing patients less than 65 years old with patients 65 years of age or older.

Tests for the equality of toxicity grade distributions and QOL assessment distributions were based on the Wilcoxon test.[11] Differences in percent of patients with PS = 0 were evaluated using Fisher's exact test.[12] The Kaplan-Meier method[13] was used to estimate DFS and OS. DFS was defined as the time from randomization to first relapse (including ipsilateral breast cancer recurrence), second primary tumor (including breast tumor), or death without relapse, whichever occurred first. OS was defined as the time from randomization to death from any cause. Multiple regression analyses using Cox proportional hazards models[14] were conducted to adjust for covariates and to test for interaction effects. Covariates included in the models were ER status, nodal status, tumor size, tumor grade, and type of primary surgery. Differences with respect to competing risks were evaluated using the cumulative incidence function method.[15] All analyses were conducted using the SAS (SAS institute Inc, Cary, NC), StatXact (CYTEL Software Corporation, Cambridge, MA), and *S*-PLUS (Mathsoft, Inc, Cambridge, MA) software packages, and all *P* values were two-sided. The median follow-up was 8.0 years.

RESULTS

Patient Characteristics

Table 1 lists patient characteristics according to treatment group and age category. None of the disease-related characteristics was significantly different between older and younger patients. There were, however, trends toward lower grade tumors ($P = .08$) and more ER-positive tumors ($P = .13$) among older patients compared with younger patients. As expected, older patients had more comorbid conditions reported than younger ($P = .001$). Within each age category, the treatment groups were well-balanced with respect to these prognostic factors.

Table 1. Patient Characteristics According to Treatment Assignment and Age Category

	Patients Age < 65 Years at Entry (%)		Patients Age ≥ 65 Years at Entry (%)	
	Tamoxifen Alone (n = 213)	Tamoxifen + CMF (n = 223)	Tamoxifen Alone (n = 93)	Tamoxifen + CMF (n = 79)
ER-positive	77	74	81	82
Nodes 1-3	64	56	63	60
Tumor Size <2 cm	69	67	70	66
Grade 1	9	12	9	15
Grade 2	29	31	30	28
Grade 3	25	17	15	6
Grade unknown	37	41	46	51
Mastectomy	75	75	76	80
Comorbid condition*	31	23	40	42

NOTE. Grade adhering to strict Bloom and Richardson criteria was available for 58% of the patients.

*Comorbid conditions were primarily hypertension, heart disease, diabetes, and arthrosis/arthritis.

Toxicity

Three of the 302 patients randomized to receive CMF did not receive any chemotherapy and have been excluded from the toxicity analyses. Table 2 lists the percent of patients who experienced each degree of toxicity (both overall toxicity and different types) according to age category. There were no grade 4 toxicities. The distributions of grades for both hematologic ($P = .0002$) and mucosal toxicities ($P = .004$) were significantly higher for patients 65 years of age or older compared with women under 65 years old. Older women had more grade 3 hematologic toxicity compared with younger women (9.2% *v* 4.5%, respectively). Leukopenia was the most common hematologic toxicity: rates of grade 3 and grade 2 leukopenia were 4% and 47% for older patients and 1% and 27% for younger patients, respectively. Four percent of older women had grade 3 mucosal toxicity compared with 0.9% of younger women.

Because there were only six cases of hepatic toxicity (all six in younger women), hepatic toxicities were combined with the category of other toxicities. Other kinds of toxicity were equally distributed in the different age categories ($P = .34$). Largely because of the differences observed for the hematologic and mucosal category, the worst grade of toxicity of any type was significantly higher for older patients than for younger patients ($P = .004$). More women 65 years of age or older had at least one grade 3 toxicity compared with patients under 65 years old (17.1% *v* 7.2%, respectively).

Table 2. Distribution of Worst Grade of Toxicity According to Type of Toxicity and Age Category for 299 Assessable Patients Who Received Some CMF Chemotherapy

	% of Patients With Hematologic Toxicity*		% of Patients With Mucosal Toxicity		% of Patients With Other Toxicity		% of Patients With Worst Grade/Any Toxicity	
Toxicity	< 65 Years Old (n = 223)	≥ 65 Years Old (n = 76)	< 65 Years Old (n = 223)	≥ 65 Years Old (n = 76)	< 65 Years Old (n = 223)	≥ 65 Years Old (n = 76)	< 65 Years Old (n = 223)	≥ 65 Years Old (n = 76)
Grade 0	12.6	9.2	72.2	55.3	15.3	18.4	3.6	2.6
Grade 1	53.4	30.3	19.3	27.6	45.3	50.0	37.7	23.7
Grade 2	29.6	51.3	7.6	13.2	36.8	25.0	51.6	56.6
Grade 3	4.5	9.2	0.9	4.0	2.7	6.6	7.2	17.1
P	.0002		.004		.335		.004	

*Type and grade of hematologic toxicity comparing younger versus older patients: leukopenia: grade 2, 27.4% *v* 47.4%, grade 3, 0.9% *v* 4.0%; anemia: grade 2, 0.5% *v* 5.3%, grade 3, 0.5% *v* 0%; neutropenia: grade 2, 3.6% *v* 4.0%, grade 3, 1.8% *v* 2.6%; hemorrhage: grade 2, 0.5% *v* 1.3%, grade 3, 0% *v* 0%; infection: grade 2, 3.1% *v* 2.6%, grade 3, 0.9% *v* 1.3%; and thrombocytopenia: grade 2, 2.7% *v* 10.5%, grade 3, 0.9% *v* 4.0%, respectively.

Two deaths related to therapy were observed in the CMF arm, one in the younger group (liver cirrhosis) and one in the older group (renal failure). A review of the deaths while under adjuvant CMF on IBCSG studies was recently published.[16]

QOL

The median QOL scores (PACIS, physical well-being, mood, and appetite) and the percent of patients with PS = 0 are listed in Table 3. These measures were not statistically significantly different between the two age groups. When comparing QOL measures of the two treatment groups, a significant difference was observed at the 3-month assessment, both overall and within each age group. This assessment corresponds to the beginning of the last cycle of CMF. Differences at other time points were not statistically significant, except for PACIS. Patients continued to report more effort to cope in the chemotherapy group compared with the tamoxifen alone group across most time points, both overall and within each group. A complete analysis of the QOL data collected during this trial can be found in Hürny et al.[9]

CMF Dose Received

The amount of CMF dose actually received was calculated for each patient and compared with the planned CMF dose for that patient. Figure 1 shows the percent of patients who at least received a given percent of protocol-specified CMF dose according to age group. Among the older patient group, 38 (48.1%) of the 79 patients received at least 85% of the protocol-specified CMF dose compared with 144 (64.6%) of the 223 women in the younger patient group ($P = .0008$ by Wilcoxon test).

DFS

Figure 2 shows the Kaplan-Meier plots of DFS for CMF + tamoxifen versus tamoxifen alone for the younger patient group, and Fig 3 shows the DFS treatment comparison for the older patients. Table 4 lists the results of the Cox model multiple regression analyses, showing the treatment comparisons overall and according to age groups. Overall, the addition of CMF to tamoxifen significantly reduced the risk of relapse, with estimated 5-year DFS percents of 62% for chemoendocrine therapy and 56% for endocrine therapy alone (hazards ratio [HR], 0.78; 95% confidence interval [CI], 62% to 97%; $P = .03$). The treatment effect was statistically significant among patients younger than 65 years at the time of study entry (HR, 0.70; 95% CI, 0.53 to 0.91; $P = .008$). In contrast, adding CMF to tamoxifen provided little advantage for the older patients (HR, 1.00; 95% CI, 0.65 to 1.52; $P = .99$). The test for heterogeneity of the CMF effect according to age group was not statistically significant ($P = .24$).

Some of the reduced effectiveness of CMF might have been caused by the increased risk of death or second primary tumor (not breast) without recurrence in the elderly. In fact, 22 older patients (13%) had such a first event compared with 25 younger patients (6%) ($P = .006$, competing risk analysis).[15] These proportions of patients were split evenly between the two treatment groups (6% in both arms for the younger patients and 13% in both arms for the older patients).

Separate analyses are also listed in Table 4 for the ER-positive and the ER-negative cohorts. The randomization was stratified by ER status, which had to be known before patient enrollment onto the trial. The results within ER subgroups were similar with respect to outcome.

OS

Table 5 lists the treatment comparisons with respect to OS. Differences in OS between the two treatment groups were not statistically significant, either overall or within subgroups defined by ER status or age. Breast cancer was the cause of death in 90% of the younger patients who died

Table 3. Performance Status Score and Median Values for Patient-Rated QOL Measures by Treatment and Age Group

	Month 1		Month 3		Month 6†		Month 12†		Month 18†	
	Score	No. of Patients	Score	No. of Patients	Score	No. of Patients	Score	No. of Patients	Score	No. of Patients
Tamoxifen + CMF										
PS										
< 65 years		NA*	88	189	92	191	90	179	91	175
≥ 65 years		NA*	84	64	90	68	85	63	93	65
PACIS										
< 65 years	60	190	67	159	79	156	80	155	81	134
≥ 65 years	59	58	68	55	83	49	85	53	82	55
Physical well-being										
< 65 years	82	194	84	159	85	155	86	158	86	133
≥ 65 years	83	57	79	53	85	49	87	53	85	55
Mood										
< 65 years	75	192	76	158	82	154	87	158	86	133
≥ 65 years	73	58	71	52	84	48	82	53	83	55
Appetite										
< 65 years	87	193	91	158	93	154	94	158	93	133
≥ 65 years	88	56	89	54	91	49	92	53	90	54
Tamoxifen alone										
PS										
< 65 years		NA*	96	191	94	188	88	170	90	169
≥ 65 years		NA*	98	84	94	84	88	75	91	71
PACIS										
< 65 years	63	175	80	137	81	142	88	131	84	124
≥ 65 years	61	66	83	57	80	65	87	59	91	57
Physical well-being										
< 65 years	82	173	86	138	85	139	86	132	87	121
≥ 65 years	78	67	89	59	87	64	89	61	87	55
Mood										
< 65 years	78	173	85	139	83	138	86	133	85	121
≥ 65 years	78	66	87	57	86	64	89	61	86	55
Appetite										
< 65 years	93	172	94	138	93	138	91	133	93	119
≥ 65 years	92	67	94	59	92	65	94	61	94	54

NOTE. PS scores represent proportion with score equal to zero, ie, fully active without restriction or aid or analgesics. Patient-rated QOL scores are median values (values are 0 to 100, with higher scores corresponding to better QOL).

*The only information available at baseline on PS was that the PS had to be ≤ 2 for patients to be eligible.

†Scores at 9 and 15 months were consistent with those reported at 6, 12, and 18 months and for brevity are not shown in the table.

(92% in the tamoxifen alone group and 89% in the CMF group) and for 75% of the older patients who died (77% in the tamoxifen alone group and 73% in the CMF group).

DFS According to Dose of CMF Received

Table 6 lists the DFS outcome according to age group and percent of expected CMF dose received. Surprisingly, with the older patient population, the patients who received less than 85% of their expected dose did not have a worse DFS than patients who received at least 85% of their expected dose. Thus, the lower effectiveness of CMF observed for the older patients could not be attributed to the higher incidence of dose reductions for this patient group.

DISCUSSION

This study has examined the toxicity encountered in elderly (≥ 65 years old) node-positive breast cancer patients who received three cycles of classic CMF chemotherapy compared with younger (< 65 years) postmenopausal breast cancer patients. We found a significant relationship between older age and increased incidence of grade 3 toxicity from adjuvant chemotherapy. There were no grade 4 toxicities, but there were two deaths recorded during chemotherapy, one in each of the two age groups. Toxic effects were increased within each category of toxicity evaluated. Special attention should be given to mucosal toxicities. Older women are at higher risk for diarrhea, cystitis, gastritis, and

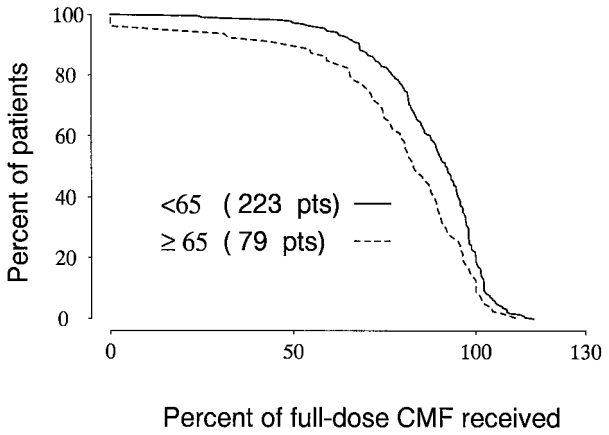

Fig 1. Percent of patients receiving at least a given percent of protocol-specified CMF dose, according to age group. Forty-eight percent of the older patients and 65% of the younger patients received at least 85% of the protocol-specified dose (P = .0008 by Wilcoxon test).

mucositis of the oral cavity. In younger patients, these toxicities are easily managed, but they can easily be fatal in older patients. For example, fluorouracil-induced diarrhea in an older patient may cause severe dehydration and failure of vascular support and may be a possible cause of death if not quickly treated. Older women may live alone, and if not advised of the risk of mucosal toxicity, they may underevaluate the symptoms and be treated when it may be too late. None of these events were documented in this clinical trial.

The drugs that are probably implicated in mucosal toxicity are methotrexate and cyclophosphamide. Assuming that impaired renal excretion of these drugs was the main factor affecting toxicity in the elderly, Gelman and Taylor[17] conducted a trial on women with advanced breast cancer aged 65 years or older in which creatinine clearance rather than surface area was used to calculate the initial doses of cyclophosphamide and methotrexate in the CMF combination. Unfortunately, this approach almost halved the response rate, with complete responses decreasing from 24% to 7% and partial responses reduced from 68% to 44%. This study confirmed data from Bonadonna et al[18] showing that the original CMF schedule given at reduced doses was associated with decreased efficacy in both metastatic and adjuvant settings. In our study, the prescribed dose of CMF was not adjusted for age, as it had been in the earlier study by Bonadonna et al.[18] Our older group of patients was probably overtreated, but the few number of cycles administered, three consecutive CMF courses instead of six (as in the Bonadonna study), limited the toxicity. Other authors[19,20] could not confirm a proper tolerance to chemotherapy in the elderly population when CMF was used in the metastatic setting. It is important to stress the fact that patients greater than 70 years old who were treated in these protocols were highly selected, with good PS and few associated comorbid conditions. This fact probably limited the toxicity encountered. In the study by Pritchard et al,[21] which was based on 705 postmenopausal patients with node-positive disease, it was concluded that the addition of CMF to tamoxifen added considerable toxicity in these women. It would have been interesting to know how many of the patients experiencing severe toxicity were older than 65 years of age.

QOL assessments in terms of PACIS score, physical well-being, mood, appetite, and PS were similar in this study for younger and older patients, indicating a comparable subjective burden of chemotherapy for these two groups. It is well known in geriatric medicine that elderly patients have a tendency to complain less and endure symptoms better.[22] This could explain the fact that the excess of objective toxicity in the group of older patients is not reflected in the self-reported measures of QOL. We conclude that with proper care, older women can tolerate CMF chemotherapy.

To date, the adjuvant trials that have been conducted specifically in elderly breast cancer patients with node-positive disease have used hormonal therapy alone with tamoxifen. An ECOG trial[23] involved 170 patients age 65 years or older randomized between tamoxifen for 2 years or placebo. Median age was 71 years; 32% were 71 to 75 years

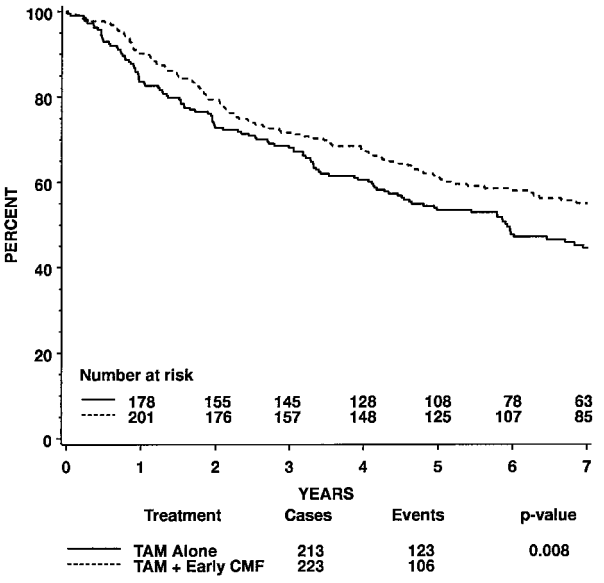

Fig 2. DFS, according to randomized treatment group, for 436 postmenopausal node-positive breast cancer patients 65 years of age. Median follow-up was 8.0 years.

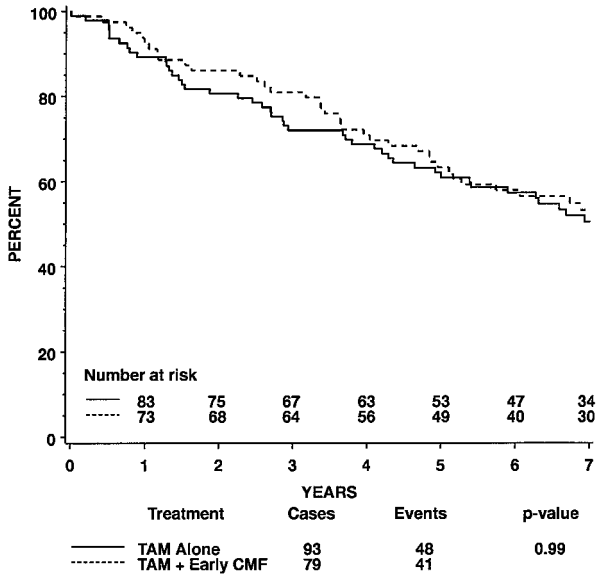

Fig 3. DFS, according to randomized treatment group, for 172 postmenopausal node-positive breast cancer patients ≥ 65 years of age. Median follow-up was 8.0 years.

old, and 21% were older than 75 years. At a median follow-up of 4 years, there was a significant benefit for the tamoxifen arm compared with the placebo arm: DFS was 73% versus 52%, respectively ($P = .003$). No treatment differences were noted in OS (80% *v* 74%, respectively; $P = .26$), but the majority of patients treated initially with placebo received tamoxifen on recurrence. This along with competing causes of death could have attenuated the survival difference. Another trial, conducted by the IBCSG,[3] involved 349 patients aged 66 to 80 years (median age, 70 years) randomized to 1 year of tamoxifen and low-dose prednisone versus no adjuvant treatment. A significant advantage in terms of DFS was demonstrated for the tamoxifen plus prednisone group compared with the group that received no adjuvant therapy at a median follow-up of 8 years (36% *v* 22%, $P = .004$). The benefit in OS was probably obscured by the competing causes of death. A third trial devoted to elderly patients was the Danish study,[24] which, out of 1,650 postmenopausal, node-positive breast cancer patients, involved 509 patients (31%) who were between the ages of 70 to 79 years. They were randomized to tamoxifen for 1 year plus radiation therapy (RT) versus RT alone. At 6 years of median follow-up, recurrence-free survival was 39% in the RT group versus 48% in the RT plus tamoxifen group ($P = .0008$). Although there were fewer local and distant metastases in patients treated with tamoxifen, a significant increase in OS was not observed.

The recent results reported by the Early Breast Cancer Trialists' Collaborative Group overview[2] showed that a longer duration of hormonal treatment (5 years of tamoxifen) gives a highly significant reduction in recurrence and improved survival for women with ER-positive (or unknown ER status) tumors. Such reduction was of similar magnitude in women both younger and older than 50 years (47% and 45% recurrence reduction, respectively; 30% and 20% mortality reduction, respectively). In the group of older patients (≥ 70 years old), many of the deaths in the 10 years of follow-up were the result of causes not related to the original breast cancer, which again probably obscures the real magnitude of the tamoxifen effect in elderly populations.

Up to now, therefore, at least for women whose primary tumors have functional hormonal receptors, tamoxifen

Table 4. DFS According to Assigned Treatment Group, Age at Study Entry, and ER Status

	CMF + Tamoxifen		Tamoxifen Alone		Cox Model Treatment Comparison*		
	No. of Patients	5-year DFS (% ± SE)	No. of Patients	5-year DFS (% ± SE)	HR	95% CI	*P*
All patients							
Total	302	62 ± 3	306	56 ± 3	0.78	0.62-0.97	.03
< 65 years old	223	61 ± 3	213	53 ± 3	0.70	0.53-0.91	.008
≥ 65 years old	79	63 ± 5	93	61 ± 5	1.00	0.65-1.52	.99
ER-positive							
Total	231	65 ± 3	239	58 ± 3	0.78	0.60-1.01	.06
< 65 years old	166	63 ± 4	164	55 ± 4	0.71	0.52-0.97	.03
≥ 65 years old	65	69 ± 6	75	65 ± 6	0.98	0.59-1.61	.93
ER-negative							
Total	71	50 ± 6	67	46 ± 6	0.75	0.48-1.19	.22
< 65 years old	57	54 ± 7	49	47 ± 7	0.64	0.37-1.12	.12
≥ 65 years old	14	36 ± 13	18	44 ± 12	0.99	0.39-2.55	.99

*Controlled for age, ER status, number of positive nodes, tumor size, grade, and type of surgery.

Table 5. OS According to Assigned Treatment Group, Age at Study Entry, and ER Status

	CMF + Tamoxifen		Tamoxifen Alone		Cox Model Treatment Comparison*		
	No. of Patients	5-year OS (% ± SE)	No. of Patients	5-year OS (% ± SE)	HR	95% CI	*P*
All patients							
Total	302	74 ± 3	306	76 ± 2	0.90	0.69-1.17	.43
< 65 years old	223	72 ± 3	213	75 ± 3	0.83	0.61-1.14	.25
≥ 65 years old	79	77 ± 5	93	80 ± 4	1.13	0.69-1.86	.62
ER-positive							
Total	231	80 ± 3	239	80 ± 3	0.87	0.64-1.20	.40
< 65 years old	166	77 ± 3	164	79 ± 3	0.86	0.59-1.25	.42
≥ 65 years old	65	86 ± 4	75	81 ± 5	0.91	0.50-1.68	.77
ER-negative							
Total	71	54 ± 6	67	64 ± 6	0.96	0.58-1.57	.86
< 65 years old	57	59 ± 7	49	59 ± 7	0.77	0.43-1.40	.40
≥ 65 years old	14	36 ± 13	18	78 ± 10	1.97	0.72-5.36	.19

*Controlled for age, ER status, number of positive nodes, tumor size, grade, and type of surgery.

alone is of substantial value.[2] An unanswered question is the value of tamoxifen in women with hormone receptor–negative tumors. In fact, among the 2,000 women in the overview with ER-poor and progesterone receptor–poor tumors, tamoxifen had no apparent effect on recurrence or mortality rates (1% in both cases), whereas in ER-poor, progesterone receptor–positive tumors (602 women) there was a recurrence reduction of 23% ($P = .05$) and mortality reduction of 9% (not significant). In these cases, the antineoplastic activity of tamoxifen may be caused by a functional ER that is not detectable. Preclinical data support the observation that the synthesis of effective progesterone receptor requires a biologically functional ER. Alternatively, as hypothesized by others, tamoxifen may enhance the production of transforming growth factor beta, a substance that opposes tumor growth from the tumor stroma.[25]

Three consecutive early courses of CMF added to tamoxifen compared with tamoxifen alone, as used in this trial, significantly improved 5-year DFS (64% *v* 57%; $P = .01$)[8] on the overall group of postmenopausal patients. The chemotherapy treatment effect was observed to be reduced for older patients, but the test for heterogeneity between older and younger women was not statistically significant.

Table 6. DFS According to Age at Entry and Percentage of Protocol-Specified CMF Dose Received for 302 Patients Assigned to CMF Plus Tamoxifen

	Patients Age <65		Patients Age ≥65	
Percent Dose Received	No.	5-Year DFS (% ± SE)	No.	5-Year DFS (% ± SE)
< 85% of CMF dose	79	57 ± 6	41	76 ± 7
≥ 85% of CMF dose	144	63 ± 4	38	50 ± 8
P	.20		.08	

Given the relatively few patients ≥ 65 years old who were enrolled onto the trial, it is uncertain whether the effectiveness of CMF in the elderly cohort is actually as modest as the data suggest. Some of the observed reduction in CMF effect among the older patients might be because of the higher proportion of patients with ER-positive tumors in this cohort, for which tamoxifen treatment is highly effective. Similarly, the greater effect of CMF among younger patients could, in part, be related to the higher proportion of patients with ER-negative tumors in this cohort. The recently reported results of the overview of polychemotherapy for early breast cancer[26] confirm the paucity of data on the treatment effect in patients aged ≥ 70 years and a gradual attenuation of effects with increasing age. The present results support the view of little impact of chemotherapy in elderly women treated with tamoxifen. As listed in Table 6, this does not seem to be caused by a dose reduction, as was hypothesized by Bonadonna and others, but is probably related to the biologic behavior of the tumor in older women, considering a better tamoxifen activity that obscures the chemotherapy effect.

In 1990, Fisher et al[27] published the results of a National Surgical Adjuvant Breast and Bowel Project trial (NSABP B-16) in node-positive postmenopausal patients who were randomized among tamoxifen alone, four cycles of doxorubicin, cyclophosphamide, and tamoxifen, or 17 cycles of melphalan, fluorouracil, and tamoxifen. At 3 years of median follow-up, a better DFS was found for patients treated with doxorubicin, cyclophosphamide, and tamoxifen when compared with those receiving tamoxifen alone (84% *v* 67%; $P = .004$). Unfortunately, it was not specified how many treated patients were older than 65 or 70 years of age. Thus, in contrast to several trials that used long-term chemotherapy (six or more cycles), two trials of tamoxifen combined with

short-term chemotherapy (three cycles of CMF, as in our trial, or four cycles of doxorubicin and cyclophosphamide, as in NSABP B-16) showed a superior outcome for the chemoendocrine therapy regimen compared with tamoxifen alone. CMF regimens are usually preferred in older women because of concern about cardiotoxicity from anthracycline-containing combinations. However, it should be noted that the trials that demonstrated a significant benefit for the addition of CMF to tamoxifen used classical CMF,[28] as originally designed and studied by Bonadonna.[18]

In conclusion, whether the addition of chemotherapy to tamoxifen provides significant clinical benefit in node-positive elderly subgroups of patients is not yet completely clarified because of the few patients randomized in clinical trials. However, available data support little impact of chemotherapy in this subset of patients. Further studies in the adjuvant setting are needed for the elderly population of postmenopausal patients.

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