Combination Hormonal Therapy With Tamoxifen Plus Fluoxymesterone Versus *Tamoxifen Alone in Postmenopausal Women With Metastatic Breast Cancer*

An Updated Analysis

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A randomized trial was performed to determine if therapy with tamoxifen (TAM) plus fluoxymesterone (FLU) was more efficacious than TAM alone for postmenopausal women with metastatic breast cancer. Patients failing TAM could subsequently receive FLU. The dose of both drugs was 10 mg orally twice daily. Objective responses were seen in 50 of 119 (42%) TAM patients and 64 of 119 (54%) TAM plus FLU patients (two-sided $P = 0.07$). Time to disease progression was better for TAM plus FLU (medians: 11.6 *versus* 6.5 months; Cox model, $P = 0.03$). Duration of response and survival were similar in the two treatment arms. Among 97 patients with estrogen receptor (ER) of 10 or greater and 65 years of age or older, there were highly significant advantages for treatment with TAM plus FLU in both response rate and time to progression. Of particular note is that in this patient group TAM plus FLU showed a survival advantage (Cox model, $P = 0.05$). Although these data require confirmation in a prospective randomized trial, they suggest that there is a substantive therapeutic advantage for TAM plus FLU over TAM alone in elderly women with ER of 10 fmol or greater. *Cancer* **67:886–891, 1991.**

TAMOXIFEN (TAM) has been considered to be the hormonal agent of first choice for management of postmenopausal women with metastatic breast cancer,[1,2] and fluoxymesterone (FLU) has known antitumor activity.[3] We previously reported[4] the results of a randomized trial comparing TAM alone with TAM plus FLU and concluded that the combination produced an advantage in terms of higher objective response rate and longer time to disease progression. However, we did not consider this advantage to be of sufficient magnitude to recommend

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the routine clinical use of this combination given the androgenic side effects encountered and the lack of survival advantage. The current report presents an update of this study with 2.5 years of additional follow-up and an exploratory analysis of these more mature data. With respect to estrogen receptor (ER) status, patients were allowed entry into this protocol providing their tumors were not known to be ER-negative. ER values of more than 3 (fmol/mg cytosol protein) were considered positive in the Mayo Laboratory until 1989 when a review of previous experience indicated that a lower bound value of 10 fmol was more appropriate[5] and led to a formal change in the designation of ER-positive. Considering the current study, it was postulated that the therapeutic value of adding FLU to TAM might be more demonstrable in women whose tumors were known to have this level of receptor. In addition, there was particular interest in the subset of patients 65 years of age or older with ER of 10 or greater. We chose age 65 because this seemed to be a reasonable boundary for the designation of elderly and corresponds to one employed in the past. The impetus for this interest was that a current emphasis of adjuvant therapy research in postmenopausal women involves comparisons of TAM with chemotherapy-containing regimens. Because many clinicians are reluctant to administer chemotherapy to elderly women and hormonal therapy may be more appropriate, the identification of a purely hormonal therapy approach that might be superior to TAM alone could have implications for study in the adjuvant setting.

Methods

The details regarding methodology have been previously presented,[4] and only salient points will be reviewed. This trial involved postmenopausal women with metastatic breast cancer who had an indicator lesion that was either measurable or evaluable. Patients with central nervous system (CNS) metastasis, malignant pleural effusions or ascites, or blastic or mixed lytic and blastic osseous metastasis as the only evidence of disease were not eligible. An ER determination was not required for entry but when known was required to be classified as positive. Patients were to have received no prior additive hormonal therapy except for prednisone when administered as part of a combination chemotherapy program, and upon entry to the study the dose of prednisone was to have been no more than 7.5 mg/dl. Patients were to have received no more than one prior chemotherapy regimen. Written informed consent was provided by each patient before entry to the study.

Patients were stratified according to ER status, menopausal status (*i.e.*, years postmenopausal *versus* prior castration), Eastern Cooperative Oncology Group (ECOG) performance score, dominant disease status, and prior chemotherapy. Patients were then randomized to treatment with either TAM alone or TAM plus FLU (supplied as Halotestin; The Upjohn Company, Kalamazoo, MI). The dose level of both agents was 10 mg orally twice daily. Patients failing TAM alone could then receive FLU, providing eligibility criteria were fulfilled and further hormonal therapy was judged to be appropriate.

Response criteria were as previously defined[4] and included traditional criteria for complete responses (CR) and partial responses (PR) in patients with measurable disease. In patients with evaluable disease, a regression (REG) was used to indicate response where there was a definite decrease in tumor size that was not quantifiable. Duration of response was defined as the time from randomization to the last date when the patient was known to have a CR, PR, or REG status. Time to progression was defined as the time from randomization to the development of progressive disease. Patients who died while in the study without known progressive disease were considered to have progressed at the date of death. Statistical methods used[6–8] are described in our initial report. With regard to multivariate modeling, the general strategy was to screen potential prognostic factors one at a time by including treatment and a given factor in the model. Those factors which had a two-sided P value (associated with their standardized regression coefficient) less than 0.20 were subsequently included in a model with a treatment factor to perform adjusted tests. Prognostic factors identified for the total group of randomized patients were also used for performing adjusted tests within specified subsets. Hazard ratios, as used in this report, indicate the relative rate of disease progression or death for TAM plus FLU patients compared with that for TAM patients. All statistical tests were two-sided.

Patient Characteristics

Two hundred forty-nine patients were entered into this study from November 1981 to June 1985, and 11 were disqualified (7 on TAM, 4 on TAM plus FLU).[4] The characteristics of the 238 eligible patients are comparable between the two treatment groups (Table 1). All of the patients with ER data except for four on TAM and six on TAM plus FLU had ER values of at least 10 fmol/mg cytosol protein by a dextran-coated charcoal technique.

Results

Randomized Portion of Study

Response: Response data are shown in Table 2 with a subdivision according to whether the patient had a measurable or an evaluable indicator lesion. The overall response rates were 42% for TAM and 54% for TAM plus FLU, and this difference approached statistical significance ($P = 0.07$). The median duration of response was equal for both regimens at 15.6 months.

When analyzed according to dominant disease status,

TABLE 1. Patient Characteristics

	TAM	TAM + FLU
No.	119	119
Age (yr)		
Median	67	67
Range	41–89	35–88
No. < 50 yr	6	8
Menopausal status (%)		
1 to <5 yr postmenopausal	9	9
>5 yr postmenopausal	81	82
Prior castration	10	9
Disease-free interval (%)		
<1 yr	42	39
1–5 yr	34	45
>5 yr	23	17
Unknown	2	0
Prior chemotherapy (%)		
Yes	14	14
ECOG (%)		
0 or 1	82	78
2 or 3	18	22
Dominant disease status (%)		
Soft tissue	16	19
Osseous	40	36
Visceral	44	45
No. of metastatic sites (%)		
1	46	55
2	43	30
3	9	13
4	2	22
Estrogen receptor (%)		
Not obtained	24	26
Positive	76	74

TAM: tamoxifen; FLU: fluoxymesterone; ECOG: Eastern Cooperative Oncology Group.

response rates for TAM and for TAM plus FLU were 68% and 83%, respectively, in soft-tissue–dominant disease; 38% and 40% in osseous-dominant disease; and 37% and 53% in visceral-dominant disease. Considering ER-positive patients only, 37 of 91 patients (41%) receiving TAM achieved a response, compared with 50 of 88 patients (57%) receiving TAM plus FLU. In those patients without hormonal receptor data, responses were seen in 13 of 28 (46%) and 14 of 31 patients (46%), respectively.

A logistic regression analysis was performed to identify factors associated with objective response. Three variables (dominant disease, disease-free interval, and measurable *versus* evaluable disease) were significant or almost significant (P values of 0.0001, 0.06, and 0.13, respectively). The treatment effect favoring TAM plus FLU over TAM alone, after adjustment for these three variables, bordered on statistical significance ($P = 0.06$).

Progression: Progression has been observed in 222 (93%) of the study patients. One patient on TAM plus FLU never had a valid reassessment and was censored at the time of entry into the study, thereby reducing the number evaluable for progression to 118. The median time to progression was 6.5 months for TAM and 11.6 months for TAM plus FLU (Fig. 1), which represents a 77% longer median time to progression for patients entered on the TAM plus FLU treatment arm. The log-rank test for equality of time to progression distributions approached statistical significance ($P = 0.06$). The hazard ratio for progression (hazard of TAM plus FLU/hazard of TAM) was 0.77 with a 95% confidence interval of 0.59 to 1.01.

Proportional hazards modeling identified four variables to be potentially prognostic for progression: number of metastatic sites ($P = 0.03$), prior chemotherapy ($P = 0.09$), disease-free interval ($P = 0.14$), and ECOG performance score ($P = 0.18$). TAM plus FLU was significantly superior to TAM alone ($P = 0.03$) after adjusting for these four variables. The adjusted progression hazard ratio was 0.75 (95% confidence interval of 0.57 to 0.98).

Survival: Eighty-two percent of the patients have died (Fig. 2). The estimated median survival time is 30.1 months for TAM and 32.2 months for TAM plus FLU. The variables determined by proportional hazards modeling to be potentially prognostic for survival were disease-free interval ($P = 0.04$), performance score ($P = 0.05$), number of metastatic sites ($P = 0.05$), and dominant disease ($P = 0.06$). There was no statistically significant difference between treatment arms in both unadjusted (log-rank $P = 0.98$) and adjusted ($P = 0.95$) analyses.

Exploratory Analysis

About one-fourth of the patients did not have ER data available, and ten patients were classified as ER-positive with an ER of 3 to 9 fmol. Since completion of this trial, the value for ER-positive in the Mayo Laboratory has been modified to a level of 10 fmol or greater.

Patients 65 Years of Age or Older With ER of 10 fmol or Greater

The patient characteristics are given in Table 3. This was an elderly group of patients with the median ages being 75 years for TAM patients and 72 years for TAM plus FLU patients, and the two groups are well balanced for the prognostic factors, including ER values.

Response: The overall response rate (CR + PR + REG)

TABLE 2. Best Response Achieved

Indicator lesion	TAM (%)	TAM + FLU (%)
No. measurable	82	84
CR	11 (13)	22 (26)
PR	27 (33)	25 (30)
CR + PR	38 (46)	47 (56)
No. evaluable	37	35
CR	3 (8)	5 (14)
REG	9 (24)	12 (34)
CR + REG	12 (32)	17 (49)
Total (CR + PR + REG)	50/119 (42)	64/119 (54)

TAM: tamoxifen; FLU: fluoxymesterone; CR: complete response; PR: partial response; REG: regression (see text).

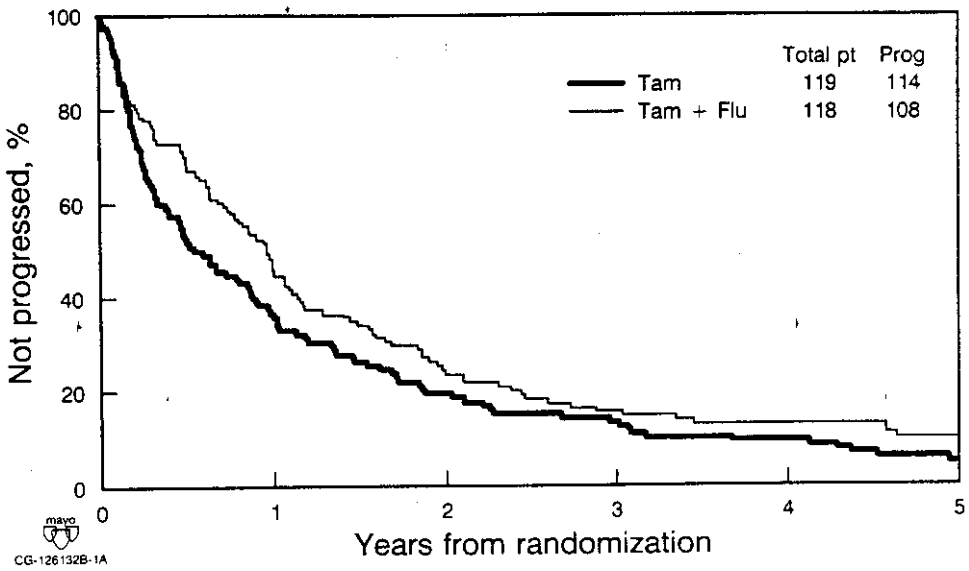

FIG. 1. Time to disease progression for patients treated with tamoxifen alone or in combination with fluoxymesterone.

for TAM plus FLU (32/47, 68%) was substantially and significantly higher than that for TAM alone (20/50, 40%) (chi-square $P = 0.006$). After adjustment for prognostic variables in logistic regression analysis, the treatment effect favoring TAM plus FLU was significant ($P = 0.004$). The median duration of response was longer for TAM plus FLU (15.8 months) than for TAM alone (12.1 months), but the distributions of duration of response were not significantly different (log-rank $P = 0.85$).

Progression: Progression has been observed in 89% of the patients in this subset (Fig 3). Patients receiving TAM plus FLU had a significantly longer time to progression (log-rank $P = 0.007$), with medians of 7.1 months for TAM and 18.3 months for TAM plus FLU. This benefit became more significant after adjusting for the four prognostic factors in a Cox model ($P = 0.002$). The adjusted progression hazard ratio was 0.49 with a 95% confidence interval of 0.32 to 0.76.

Survival: Seventy-eight percent of the patients in this subset have died (Fig. 4). The median survivals were 27.8 months for TAM and 42.9 months for TAM plus FLU, and the log-rank test approached significance ($P = 0.11$). After adjusting for prognostic factors in a Cox model, the improved survival for TAM plus FLU approached statistical significance ($P = 0.06$). The adjusted death hazard ratio was 0.64 with a 95% confidence interval of 0.41 to 1.02.

All Patients With ER of 10 fmol or Greater

The overall response rate for TAM plus FLU (50/82, 61%) was significantly greater than for TAM alone (36/86, 42%) (chi-square $P = 0.01$) and was highly significant ($P = 0.008$) after adjustment for prognostic variables in logistic regression analysis. The median time to progression was significantly longer for TAM plus FLU (12.9 months) than for TAM alone (7.4 months), and the log-

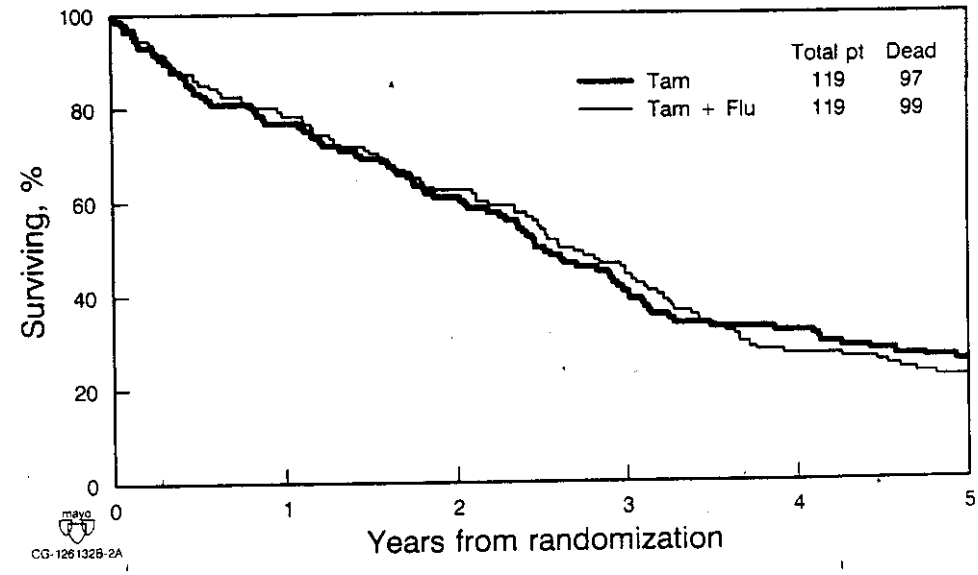

FIG. 2. Survival of patients treated with tamoxifen alone or in combination with fluoxymesterone.

TABLE 3. Characteristics of Patients 65 Years of Age or Older and With ER ≥ 10 fmol

	TAM	TAM + FLU
No.	50	47
Age (yr)		
Median	75	72
Range	65–89	65–88
Disease-free interval (%)		
<1 yr	46	51
1–5 yr	40	38
>5 yr	12	11
Unknown	2	0
Prior chemotherapy (%)		
Yes	10	6
ECOG (%)		
0 or 1	74	77
2 or 3	26	23
Dominant disease status (%)		
Soft tissue	22	23
Osseous	34	32
Visceral	44	45
No. of metastatic sites (%)		
1	50	49
2	36	34
3	10	15
4	4	2
Indicator (%)		
Measurable	70	68
Evaluable	30	32
Estrogen receptor*		
Median	144	132
Range	11–1215	11–1510
10–<50	24%	28%
≥50–<100	22%	15%
≥100	54%	57%

TAM: tamoxifen; FLU: fluoxymesterone; ECOG: Eastern Cooperative Oncology Group.
* fmol/mg cytosol protein.

rank test was significant ($P = 0.01$). After adjusting for prognostic factors in a Cox model, the test for treatment favored TAM plus FLU and was highly significant ($P = 0.004$). The adjusted progression hazard ratio was 0.61, with a 95% confidence interval of 0.44 to 0.85. There was no significant difference in survival (log-rank $P = 0.28$), with median survival times of 36.9 months for TAM plus FLU and 29.8 months for TAM alone. After adjustment for prognostic factors in a Cox model, the test for treatment effect remained nonsignificant ($P = 0.21$).

Secondary Treatment

Fifty-three patients receiving FLU after failure on TAM alone have been assessed. The overall response rate was 40%, and it was 47% (14 of 30) among the prior TAM responders and 30% (7 of 23) among the prior TAM nonresponders. From the date of initiation of FLU therapy, median time to progression was 6.3 months and median survival was 25.6 months. Among the 31 women 65 years of age or older with ER of 10 or greater, the overall response rate to FLU was 42%.

Toxicity

In the randomized portion of the study there was a higher incidence of skin problems (mostly oily skin and some erythema), hoarseness, edema, and alopecia in patients receiving TAM plus FLU (Table 4). Otherwise, the toxicities of nausea, emesis, and hot flushes were not significantly different between the two regimens. Considering all these toxicities, they were judged to be severe in only 14 (6%) instances. Weight gain was assessed by measuring the percentage of weight gain using entry weight as baseline. On TAM, 10% had a 5% to 10% gain and 6% had a >10% gain, whereas the corresponding weight gains on TAM plus FLU were 17% and 10%, respectively. This difference in weight gain was not significant ($P = 0.16$).

Discussion

A review of this updated analysis and comparison with the report 2.5 years ago show that the superiority of TAM plus FLU over TAM alone has become stronger. Despite

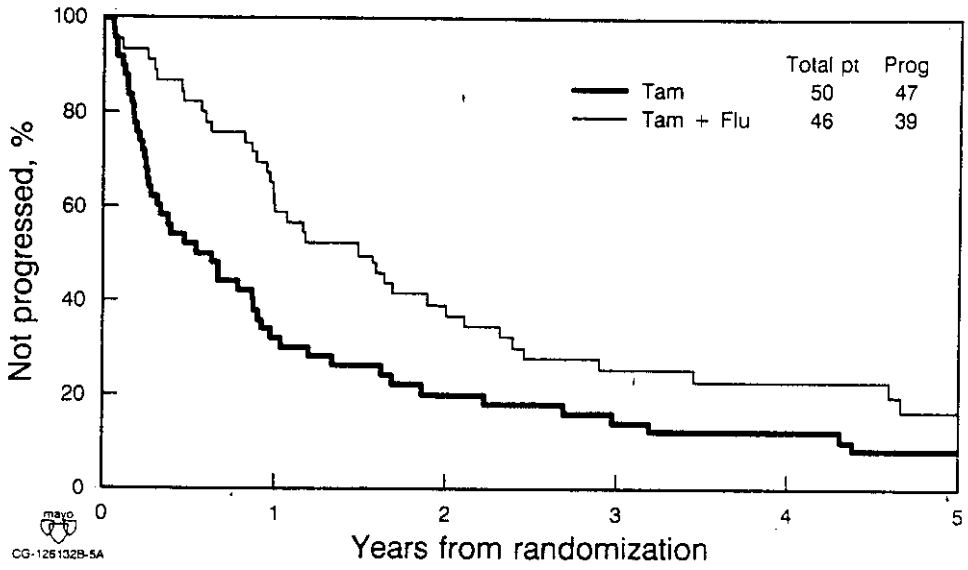

FIG. 3. Time to disease progression for patients 65 years of age or older and ER of 10 or greater treated with tamoxifen alone or in combination with fluoxymesterone.

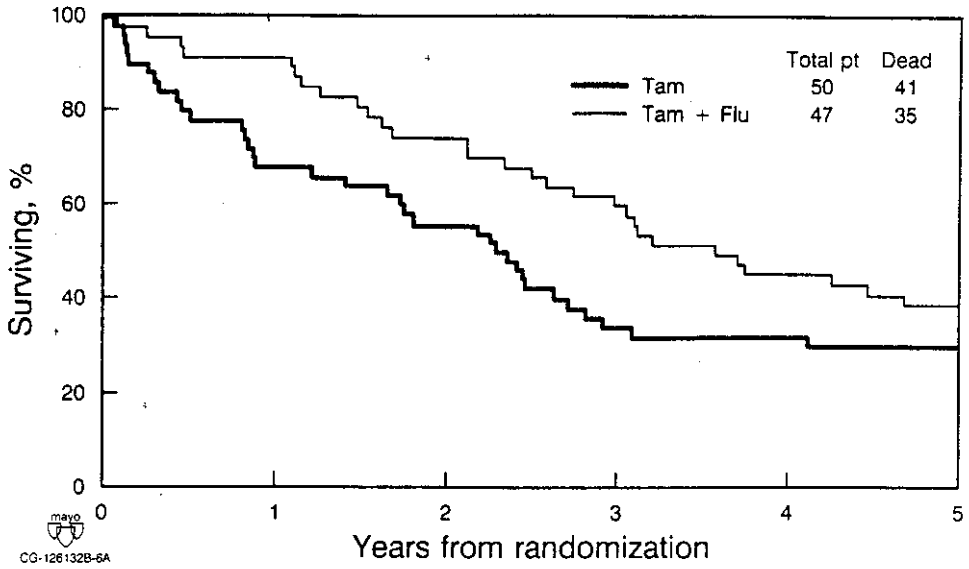

FIG. 4. Survival of patients 65 years of age or older and ER of 10 or greater treated with tamoxifen alone or in combination with fluoxymesterone.

this, the superiority of response rate and time to progression only borders statistical significance. These findings support our original conclusion that the advantages observed are indicative of a real biologic effect of adding FLU to TAM.

Subset analysis must be interpreted with caution and must be considered of value primarily for hypothesis development. Although we have purposely limited such analyses in the past, the current subset analysis was considered appropriate because of the possibility that the receptor-unknown patients, many of whom were probably ER-negative, and those with ER of less than 10 would confound the outcome by diluting any therapeutic advantage provided by the addition of FLU to TAM in patients with ER of 10 or greater. In our subset analysis of all patients with ER of 10 or greater, time to progression was significantly better for patients treated with TAM plus FLU. This advantage is especially striking in the patients 65 years of age and older, where the median time to progression was more than 2.5 times longer for the patients treated with TAM plus FLU than for those treated with TAM alone. Most important, the survival was longer for the combination approach within this elderly population, almost reaching conventionally accepted statistical significance. This survival advantage was achieved even though therapy with FLU alone was permitted after failure on TAM. Rose *et al.*[9] found a higher response rate for TAM plus FLU than for TAM alone, but there was no difference in time to treatment failure or survival,[10] and, we are not aware of any other analyses within this elderly, ER of 10 or greater subset.

Although the findings of this current analysis are provocative, the establishment of superiority in this subset of patients for the combination of TAM plus FLU would require a prospective randomized trial. Because of the direct implications of delaying progression and increasing survival in elderly women, we have developed a comparative clinical trial evaluating the addition of FLU to TAM in the adjuvant setting.

TABLE 4. Toxicity

	Percent TAM (n = 119)	Percent TAM + FLU (n = 118)	*P* value
Nausea	13	14	NS
Emesis	3	7	NS
Hot flushes	16	13	NS
Edema	12	21	0.05
Alopecia	2	14	<0.0001
Skin	0	24	<0.0001
Hoarseness	0	43	<0.0001

TAM: tamoxifen; FLU: fluoxymesterone; NS: not significant.

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