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Clinical trial

Randomized trial of tamoxifen alone or combined with fluoxymesterone as adjuvant therapy in postmenopausal women with resected estrogen receptor positive breast cancer. North Central Cancer Treatment Group Trial 89-30-52

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Summary

Purpose. This clinical trial evaluated the addition of fluoxymesterone (Flu) to tamoxifen (Tam) in women with resected early stage breast cancer and attempted to corroborate the findings of superiority for the combination over Tam alone seen in a previous randomized trial in metastatic disease.

Patients and methods. Postmenopausal women with early stage breast cancer that was known to be estrogen receptor (ER) positive were randomized to treatment with Tam (20 mg per day orally for 5 years) alone or combined with Flu (10 mg orally twice per day for 1 year). The primary endpoint was relapse-free survival (RFS) defined as local-regional or distant recurrence including ductal carcinoma *in situ* of the ipsilateral, but not contralateral breast, and death from any cause.

Results. There were 541 eligible patients entered between 1991 and 1995 and the treatment arms were balanced with respect to patient characteristics. The median follow up of patients still alive was 11.4 years. No significant difference was found between Tam plus Flu and Tam alone in terms of RFS or overall survival. The adjusted hazard ratio (Tam + Flu/Tam) for relapse or death without relapse was estimated to be 0.84 (95% CI: 0.64–1.10) and that for death was 0.89 (95% CI: 0.67–1.18). As expected there was more virilization in women who received Flu.

Conclusions. This clinical trial did not demonstrate superiority of Tam plus Flu over Tam alone as adjuvant therapy for postmenopausal women with resected early breast cancer known to be ER positive.

Introduction

Combination hormonal therapy is attractive because of the potential for increased efficacy when two agents with different mechanisms of action are employed. Several decades ago we performed a clinical trial in women with advanced breast cancer to determine if the combination of the selective estrogen receptor modulator tamoxifen (Tam) plus the androgen fluoxymesterone (Flu) was superior to tam alone [1]. Our trial in advanced disease was performed because of the report of superiority of Tam plus Flu over Tam alone, in terms of response rate and time to treatment failure, in a randomized trial in advanced breast cancer performed by Tormey et al. [2] evaluating escalating doses of Tam with or without a fixed dose of Flu. Flu had been chosen for study because of the observation that some breast cancers contained the androgen receptor (AR) [3]. Thus, the hypothesis was that the combination would be superior because Tam would target the estrogen receptor (ER) and Flu would target the AR. An updated report of our trial [1] with 93% of patients experiencing disease progression and 82% death showed an advantage for Tam plus Flu in terms of a higher response rate (54% versus 42%, 2-sided $p = 0.06$ after adjustment for factors associated with response) and longer time to disease progression (medians, 11.5 versus 6.5 months, $p = 0.03$ after adjustment for factors associated with progression). Of the 238 patients enrolled, about one-quarter did not have ER data available and 4.2% of patients had an ER in the 3–9 fmol/mg cytosol protein range. As there was a substantial proportion of patients whose tumors were ER unknown or in the borderline ER positive range of

3–9 fmol which might confound the comparison of therapies, a subset analysis was performed in the women whose tumors had an ER≥10 fmols and were definitely positive. In this 168 patient subset, the response rate was significantly better for Tam plus Flu than Tam alone (61% versus 42%, adjusted $p = 0.008$) as was the time to progression (medians, 12.9 versus 7.4 months; adjusted $p = 0.004$). There was also an advantage in survival (medians, 36.9 versus 29.8 months) but this was not significant ($p = 0.21$). Subset analyses must be interpreted with caution but are of value for developing hypotheses. However, the finding of a significant advantage in time to progression for adding Flu to Tam in the entire population and the even greater level of benefit seen in those women whose tumors were known to be ER positive provided the impetus to examine the addition of Flu to Tam in another population. The population chosen was women with resected early stage breast cancer known to be ER positive and the study was powered based upon the hazard ratio for progression observed in the subset of patients with ER≥10 fmol in the metastatic disease trial discussed above [1].

Patients and methods

Eligibility

This trial involved postmenopausal women with histologic confirmation of primary adenocarcinoma of the breast. Eligibility criteria for stage of disease, using post surgical resection-pathologic stage according to definitions of the American Joint Committee on Cancer [4], was related to age. Women with node-negative status could be any age providing the stage was T_1c (tumor size >1–2 cm) or T_2 N_0M_0 whereas those with node-positive disease were required to be at least 65 years of age and stage T_1 or T_2 N_1M_0. A woman was considered postmenopausal if one of the following held: her last menstrual period (LMP) was greater than 12 months prior to diagnosis of breast cancer or her LMP was 4–12 months prior to diagnosis of breast cancer and her follicle stimulating hormone (FSH) level was in the postmenopausal range or her FSH was in the postmenopausal range following discontinuation of estrogen replacement therapy or she had undergone a bilateral oophorectomy at least 2 months prior to the diagnosis of breast cancer or she was greater than 60 years old and had undergone a prior hysterectomy without oophorectomy (H) or she was 60 years of age or younger who had a H and FSH was in the postmenopausal range.

Patients must have undergone a modified radical mastectomy or breast conservation therapy including lumpectomy, axillary dissection, and radiation therapy. Patients who underwent lumpectomy must have had a primary tumor no larger than 5 cm and the surgical margins must have been microscopically free of tumor. The axillary dissection must have involved removal and examination of at least six axillary nodes. Patients undergoing lumpectomy were to receive whole breast radiotherapy to a dose of 50.4 Gy in 28 fractions with a 10–11 Gy boost to the lumpectomy site with an electron beam or interstitial implantation. Patients with axillary nodes involved with tumor also were to received radiotherapy (50.4 Cy) to the axillary and supraclavicular regions. Estrogen receptor (ER) assay must have been at least 10 fmol/mg cytosol protein by a standard biochemical assay or positive by an immunohistochemical assay. The interval between definitive surgery and randomization must have been 6 weeks or less.

Contraindications to entry onto this protocol included: pectoral fascia invasion, bilateral or previous breast cancer, other cancers with exception of resected non-melanoma skin cancer or adequately treated carcinoma *in-situ* of the uterine cervix unless disease-free for at least 5 years, white blood cell count less than 3000/μl, platelet count less than 100,000/μl, total bilirubin or aspartate aminotransferase over 1.5 times the institutional upper limit of normal (IULN), creatinine over 2 times the IULN and warfarin therapy. Prior systemic therapy for breast cancer was not allowed except in the case of tamoxifen providing the tamoxifen had been administered for no more than 14 days prior to randomization. This trial was approved by all participating institution's local institutional review boards and in accord with assurances filed with an approved by the Department of Health and Human Services. Written informed consent was provided by each patient before entry on study.

Evaluations and treatment plan

Within 10 days of study entry, patients underwent an evaluation that included a medical history, physical examination, hemoglobin, leukocyte count, platelet count, chemistries (which included calcium, total bilirubin, aspartate aminotransferase, alkaline phosphatase, and creatinine). Radiographic studies that were required included a chest X-ray within 1-month prior to entry and a mammogram and bone scan within 2 months prior to entry. Patients were randomized to either tamoxifen, 20 mg orally each day for 5 years or tamoxifen (Tam), 20 mg orally each day for 5 years plus fluoxymesterone (Flu) (supplied as Halotestin by Pharmacia and Upjohn Company, Kalamazoo, MI), 10 mg orally twice per day for 1 year. A dynamic allocation procedure was used to balance, between treatment arms, the marginal distributions of axillary lymph node status (number of positive nodes: zero versus 1–3 versus 4–9 versus 10 or more), age (less than 65 years versus 65 or greater), primary tumor size (less than 3 cm versus 3 cm or more), ER status (10–49 fmol versus 50 fmol or greater versus positive by immunohistochemical assay) and local therapy (mastectomy versus breast conservation therapy).

Dosage modification criteria were utilized for Flu-related toxicities. A moderate increase in facial and/or

body hair (grade 2 hirsutism) or a lowering of the voice associated with difficulty in speaking for long periods (grade 3 deepening of voice) resulted in a decrease in Flu dosage to 5 mg twice daily and, if there was no improvement after 6 months, a further reduction to 2 mg twice daily was to be made. Scalp hair loss perceptible on casual inspection was an indication for discontinuation of Flu. Erythrocytosis with a hemoglobin over 18 g/dl called for a decrease in Flu dose to 5 mg twice daily. If the hemoglobin remained over 18 g/dl after 2 months at the 5 mg dose, Flu dose was to be reduced to 2 mg twice daily. If the hemoglobin remained elevated for 2 additional months at the 2 mg dose level, the Flu was to be discontinued. Tetracycline 250 mg twice daily was to be employed if acne developed.

After initiation of therapy, patients were to be assessed every 4 months for 1 year, every 6 months during the next 4 years and annually after 5 years. At each assessment a history, physical examination, white blood cell count, hemoglobin, platelet count, serum calcium, alkaline phosphatase, aspartate aminotransferase, total bilirubin, creatinine, and chest X-ray were performed. Mammograms and pelvic examinations were performed on an annual basis. Bone scans and liver imaging were to be repeated as clinically indicated. Patients continued to receive treatment according to protocol specifications if there was no evidence of excessive toxicity or recurrent or metastatic disease. Women who developed a second breast cancer in the contralateral breast would continue therapy per protocol if the second breast cancer was stage I and occurred within 2 years of study entry. Women who developed a second non-breast primary could continue as per protocol unless an alternative therapy was more appropriate.

Study design and statistical analysis

The primary endpoint of this trial was relapse-free survival (RFS). The distribution of survival times and the toxicity profile of each treatment regimen were also examined. Relapse-free survival was defined as the time from randomization to documentation of any recurrence (local-regional or distant) of breast cancer or death from any cause without the documentation of a recurrence of breast cancer. The occurrence of ductal carcinoma *in situ* (DCIS) in the ipsilateral breast was considered an event. Disease in the contralateral breast was considered a new primary and new primaries were not considered a relapse. Patients alive without a recurrence were censored at the date of their last disease evaluation.

Disease-free survival (DFS) was defined as the time from randomization to documentation of the first of the following events: any recurrence (local, regional or distant) of breast cancer, the documentation of contralateral breast cancer, or death due to any cause. Patients who were alive without a breast recurrence, contralateral breast cancer or a second non-breast primary cancer were censored at the date of their last disease evaluation. Patients who developed a second primary (prior to breast recurrence or a contralateral breast cancer) were censored on the date the second primary was diagnosed.

Overall survival (OS) was defined as the time from registration to death due to any cause. The study was designed under the assumption that the 5-year relapse-free survival rate with Tam was 75%, the accrual rate would be 129 patients per year for 4 years, and the follow-up period after accrual was completed would be 5 years. A two-sided $\alpha = 0.05$ logrank test would then have a power of 0.80 to detect an increase of 10% in the 5-year relapse-free survival rate with the addition of Flu.

The distributions of RFS and OS times for each treatment regimen were estimated using the Kaplan–Meier method. Patient and disease characteristics examined for their potential association with RFS and OS included: age 65 years or greater (yes versus no), extent of surgery (mastectomy versus breast conserving), estrogen receptor status (10–49 fmols versus 50+ fmols versus positive), number of positive nodes (represented as 3 indicator variables for 1–3, 4–9, and 10+ positive nodes), tumor size 3 cm or greater (yes versus no), and prior exposure to exogeneous estrogens (yes versus no). A log rank test and a univariate Cox's proportional hazard model were used to assess whether the distributions of RFS or OS differed with respect to treatment or any one of these potential prognostic factors. For each endpoint, multivariate Cox's proportional hazard modeling was performed to obtain a subset of the potential prognostic factors which provided an adequate fit to the data. Residual plots were examined. A likelihood ratio test was performed to assess whether treatment made a significant contribution to the model.

Results

Patient characteristics

Five hundred forty-one patients were entered on this study between January 1991 and April 1995. Twenty-two patients (4.1%) were found to be ineligible (10 assigned to Tam and 12 assigned to Tam plus Flu) due to tumor size (7 patients), <65 years old with node positive disease (6 patients), metastatic disease at randomization (3 patients), inadequate surgical procedure (2 patients), pectoral fascia invasion (1 patient), second primary (1 patient), ER negative (1 patient), and elevated aspartate aminotransferase (1 patient). Five patients randomized to Tam + Flu cancelled their study participation prior to receiving treatment. The remaining 514 (256 on Tam and 258 on Tam + Flu) eligible patients are included in this report. The pretreatment characteristics for these patients are given in Table 1.

Clinical outcome status

At last contact, 322 patients were still alive, over 98% of these patients have been followed for at least 5 years.

Table 1. Patient characteristic at randomization

Patient characteristics	TAM ($n=256$) (%)	TAM + FLU ($n=258$) (%)
Age		
< 65 years	29.3	28.7
Prior hysterectomy	42.2	40.3
Prior BSO	24.2	21.7
Exogenous estrogens	16	19
ECOG performance status		
0	87.9	88.0
1	10.9	12.0
2	1.2	
Extent of surgery		
Mastectomy	81.6	83.3
Breast conservation	18.4	16.7
Estrogen receptor		
10–49 fmols	19.9	19.4
50+ fmols	66.4	65.5
Positive	13.7	15.1
Tumor size		
< 3 cm	78.9	78.7
≥3 cm	21.1	21.3
Number of positive nodes		
0	62.5	62.0
1–3	25.0	25.2
4–9	8.2	8.1
10+	4.3	4.7

Table 2. Sites of recurrence and second primary disease

	TAM ($n=256$)	TAM + FLU ($n=258$)
Site of recurrent disease		
Breast/mastectomy site	5	3
Lymph, axillary, or supraclavicular nodes	4	5
Chest wall	6	3
Bone	12	8
Lung	7	6
Liver	3	7
Soft tissue	1	1
Mediastinum	0	1
Intra-abdominal	1	1
Multiple sites	12	9
Site of second primary disease		
Contralateral breast disease	13	9
Colorectal cancer	4	5
Lung	3	4
Bladder	0	2
Endometrial cancer	0	2
Kidney	0	2
Lymphoma	0	2
Melanoma	2	0
Tongue	2	0
Other (singletons)	7	2
Unknown	0	1

The median length of follow-up for the patients still alive is 11.4 years (range: 1.9–14.4 years). On the Tam arm, 129 patients are alive not having recurred, 13 are alive having recurred, 14 are alive with a second primary, 47 died without recurring, 36 recurred and died, 15 have developed a second primary and died, and 2 have recurred, developed a second primary, and died. On the Tam + Flu arm, 147 patients are alive not having recurred, 5 are alive having recurred, 11 are alive with a second primary, 3 are alive having recurred and developed a second primary, 46 died without recurring, 31 recurred and died, 10 have developed a second primary and died, and 5 have recurred, developed a second primary, and died. The sites of recurrence and second primaries are presented in Table 2. The cause of death was breast cancer in 67 patients (34 on Tam alone); other cause in 100 patients (51 on Tam alone); and unknown in 25 patients (15 on Tam alone).

Relapse-free survival (Figure 1)

The 5 and 10 year RFS rates were estimated to be 84% (95% CI: 80–89%) and 67% (95% CI: 61–73%), respectively, on the Tam + Flu arm and 81% (95% CI: 76–86%) and 63% (95% CI: 58–70%), respectively, on the Tam arm. There was no evidence to suggest that the distribution of relapse-free survival times differed with respect to treatment (log-rank $p=0.261$). Univariately, age greater than 65 years (log-rank $p<0.001$), node positive disease (0 versus 1–3 versus 4–9 versus10+; log-rank $p<0.001$), and tumor size ≥3 cm (log-rank $p<0.001$) were associated with decreased relapse-free survival. Cox multivariate modeling revealed that age greater than 65 years, node-positive disease and primary tumor size ≥3 cm were significantly associated with poorer RFS. After adjusting for these factors, there was no evidence to suggest that RFS differed with respect to treatment ($p=0.215$). The adjusted hazard ratio of Tam + Flu/Tam was estimated to be 0.84 (95% CI: 0.64–1.10).

Disease-free survival (Figure 2)

The 5 and 10 year DFS rates were estimated to be 84% (95% CI: 80–89%) and 67% (95% CI: 61–73%), respectively, on the Tam + Flu arm and 78% (95% CI: 73–83%) and 61% (95% CI: 56–68%), respectively, on the Tam arm. There was no evidence to suggest that the distribution of DFS times differed with respect to treatment (log-rank $p=0.161$). Univariately, age greater than 65 years (log-rank $p<0.001$), node positive disease (0 versus 1–3 versus 4–9 versus10+; log-rank $p<0.001$), tumor size ≥3 cm (log-rank $p=0.004$) , and mastectomy (log-rank $p=0.048$) were associated with decreased DFS. Cox multivariate modeling revealed that age greater than 65 years, node positive disease (yes versus

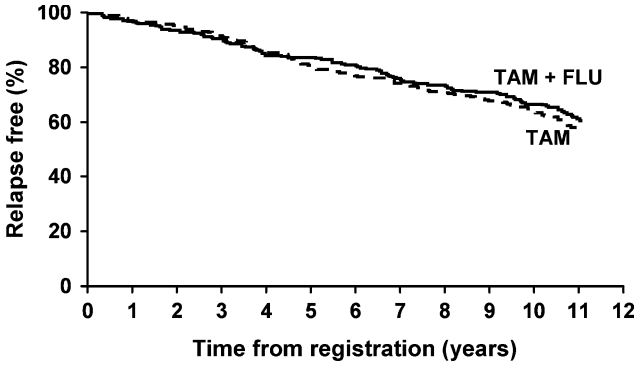

Figure 1. Relapse-free survival distributions for women treated with tamoxifen alone or tamoxifen plus fluoxymesterone.

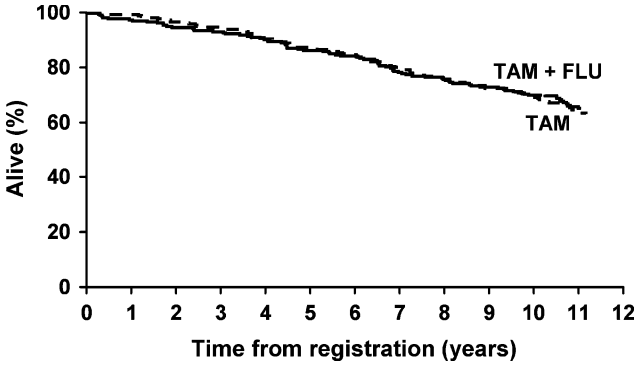

Figure 3. Overall survival distributions for women treated with tamoxifen alone or tamoxifen plus fluoxymesterone.

no) and primary tumor size ≥3 cm were significantly associated with poorer DFS. After adjusting for these factors, there was no evidence to suggest that DFS differed with respect to treatment ($p = 0.107$). The adjusted hazard ratio of Tam + Flu/Tam was estimated to be 0.80 (95% CI: 0.61–1.05).

Overall survival (Figure 3)

The 5 and 10 year OS rates were estimated to be 87% (95% CI: 83–91%) and 68% (95% CI: 63–75%), respectively, on the Tam + Flu arm and 87% (95% CI: 83–91%) and 71% (95% CI: 63–75%), respectively, on the Tam arm. There is no evidence to suggest that the distribution of survival times differed with respect to treatment (log-rank $p = 0.444$; HR [Tam + Flu/Tam] = 0.90; 95%CI: 0.67–1.19). Univariately, age greater than 65 years log-rank $p < 0.001$), number of positive nodes (0 versus 1–3 versus 4–9 versus10 + ; log-rank $p < 0.001$), and tumor size ≥3 cm (log-rank $p = 0.002$) were associated with decreased survival. Cox multivariate modeling revealed that age greater than 65 years, node-positive disease and primary tumor size ≥3 cm were significantly associated with poorer OS. After adjusting for these factors, there was no evidence to suggest that OS differed with respect to treatment ($p = 0.410$). The adjusted hazard ratio of Tam + Flu/Tam was estimated to be 0.89 (95% CI: 0.67–1.18).

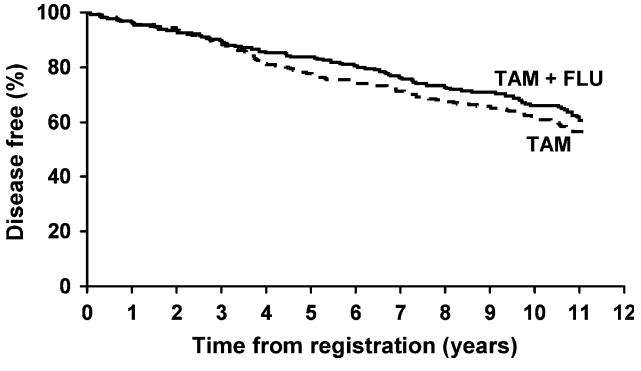

Figure 2. Disease-free survival distributions for women treated with tamoxifen alone or tamoxifen plus fluoxymesterone.

Adverse events

The most common toxicities reported in each treatment arm are given in Table 3. The proportion of patients from each treatment arm reporting hot flashes or changes in libido were similar. As expected, there were significantly more androgen-related side effects (deep voice, hirsutism, dermatitis, and male pattern baldness) were reported among those receiving Tam plus Flu. Impact of treatment on libido was prospectively collected and the incidence of increased libido and decreased libido was the same for patients receiving Flu.

Discussion

Androgen receptors have been found to be frequently expressed in human breast cancers. Moinfar et al. [5], using immunohistochemical staining in ER-positive invasive breast carcinomas, recently reported that AR-positivity was seen in 18/20 (90%) grade 1 tumors, 22/28 (76%) grade 2 tumors and 6/8 (75%) grade 3 tumors. Androgens have been shown to have antitumor efficacy in metastatic breast cancer. In 1958, Kennedy [6] concluded that fluoxymesterone was the androgen of choice on the basis of its oral formulation and less masculinizing effects compared to those previously reported with testosterone proprionate [7].

Our previous study [1] found that the addition of Flu to Tam was associated with an increased response and time to progression over Tam alone in advanced breast cancer. Rose et al. [8], however, did not identify an advantage for the combination of Tam plus Flu over Tam alone in women 65 years of age or older with a first recurrence of metastatic disease. One limitation of the study by Rose et al. is that over two-thirds of their patients had tumors with the ER status unknown and about 12% had tumors that were ER negative.

In our current trial we were unable to corroborate the level of benefit for the addition of Flu to Tam we had previously seen in the metastatic setting [1]. By contemporary standards, the sample size is small for a trial of endocrine adjuvant therapy but the sample size

Table 3. Most common toxicities reported

Toxicity	TAM ($n=256$)		TAM + FLU ($n=258$)	
	Any (%)	Grade 3+(%)	Any (%)	Grade 3+(%)
Hot flashes	62	6	67	8
Deep voice	3	0	66	12
Hirsutism	5	0	63	3
Dermatitis	8	0	35	0
Edema	22	2	30	1
Male pattern baldness	7	0	29	1
Neuro-mood	12	0	18	2
Nausea	11	0	17	0
Headache	7	0	16	1
Lethargy	7	0	10	0

was determined on the basis of the hazard ratio seen in our previous trial in metastatic disease. The hazard ratios seen in this trial all favor the Tam plus Flu regimen but are not nearly significant nor nearly what was observed in the previous trial with metastatic disease [1].

In conclusion, we were not able to corroborate the superiority of the combination of Tam plus Flu over Tam alone, when given as adjuvant hormonal therapy in early breast cancer, at a level comparable to that observed in the metastatic setting in our previous randomized trial.

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