A Randomized Trial of Tamoxifen Alone or Combined with Octreotide in the Treatment of Women with Metastatic Breast Carcinoma

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BACKGROUND. Tamoxifen (TAM) is generally considered the hormonal agent of choice for postmenopausal women with hormone receptor positive breast carcinoma. The somatostatin analogues, including octreotide, have demonstrated inhibition of breast carcinoma cell lines and multiple endocrinologic actions, including reduction of insulin-like growth factor I (IGF-I), a potent mitogen for breast carcinoma cells. In an attempt to improve the efficacy of TAM, this randomized trial was performed.

METHODS. One hundred thirty-five eligible postmenopausal women with metastatic breast carcinoma were randomized to TAM (10 mg twice daily) alone or combined with octreotide 150 μg (administered subcutaneously thrice daily). The two groups were well balanced, except the TAM group had higher proportions of patients with visceral disease (50% vs. 37%) and a disease free interval longer than 5 years (47% vs. 34%). A cohort of 18 patients was evaluated for the impact of treatment on serum IGF-I, free IGF-I, IGF binding protein 3 levels, and total IGF binding capacity.

RESULTS. The median time to progression was estimated to be 14.2 months with TAM and 10.3 months with TAM plus octreotide. The distribution of progression free survival times revealed no significant difference ($P = 0.26$), and the progression hazard ratio (TAM/TAM + octreotide) was 0.81 (95% confidence interval [CI], 0.56–1.17). The distribution of survival times revealed no significant difference ($P = 0.92$), and the death hazard ratio was 0.98 (95% CI, 0.62–1.55). When the 106 patients with measurable or evaluable disease were considered, the objective response rate was 49% with TAM alone and 43% with TAM plus octreotide ($P = 0.70$). Patients who received TAM plus octreotide had higher incidences of nausea, diarrhea, and steatorrhea. The percentage of decline in serum IGF-I, from pretreatment levels to those following 3–6 weeks of treatment, was significantly greater ($P < 0.01$) with TAM plus octreotide than with TAM alone.

CONCLUSIONS. There is no indication that the combination of TAM plus octreotide as administered in this study is substantially more efficacious than TAM alone in the treatment of postmenopausal women with metastatic breast carcinoma. The limited cohort included in IGF-I studies suggests that TAM plus octreotide produces a significantly greater reduction in serum IGF-I levels. ***Cancer* 1999;85: 1284–92.** © *1999 American Cancer Society.*

KEYWORDS: breast carcinoma, metastatic, postmenopausal, hormonal, tamoxifen, octreotide, insulin-like growth factor I.

Tamoxifen (TAM), the hormonal agent of choice for postmenopausal women with breast carcinoma, produced an objective response rate of 43% in 248 women with measurable metastatic disease in 4 consecutive prospective clinical trials.[1] Despite the clear antitumor activity of TAM, there is a need to identify more efficacious hormonal regimens.

At the time of development of this trial, it was clear that multiple hormones and growth factors could impact on breast carcinoma growth.[2] We became interested in the study of somatostatin analogues for the following reasons. Several groups of investigators had reported that somatostatin analogues, including octreotide, demonstrated inhibition of breast carcinoma cells in cultures.[3–5] Octreotide had been found to inhibit the secretion of multiple substances,[6] including growth hormone and insulin-like growth factor I (IGF-I) in acromegaly.[7] Attention was focused on IGF-I, as it is a potent mitogen for breast carcinoma cells.[8,9]

Following the demonstration by Pollak et al.[10] in a placebo-controlled, randomized trial that TAM was associated with a significant reduction in serum IGF-I levels, we hypothesized that the combination of TAM plus octreotide would provide a greater reduction in IGF-I levels than TAM alone. On this basis, we added an ancillary study to address this question while the trial was in progress.

Based on the likely importance of mitogenic peptides in addition to estradiol in breast carcinoma, the endocrinologic actions of somatostatin analogues, and evidence of their inhibition of breast carcinoma cell lines and experimental tumors, we proceeded with the following randomized trial. Initially, patients were randomized to TAM alone, octreotide alone, or the combination. The octreotide alone arm was dropped early in the study; it was found to be associated with a short time to disease progression and produced no objective responses in 10 patients.[11] This report presents the results of the randomization between TAM alone and TAM combined with octreotide.

METHODS

This trial involved postmenopausal women with progressive metastatic breast carcinoma (according to the American Joint Committee on Cancer[12]) who fulfilled the following eligibility criteria. Patients were required to have histologically confirmed breast carcinoma and histologic or cytologic proof of metastatic disease, except in the case of multiple pulmonary nodules that were known to be new, or unequivocal radiologic evidence of multiple bone metastases. Patients must have been postmenopausal, that is, must have had no menstrual period for at least 12 months in the case of a natural menopause, or castration in the case of a prior premenopausal status. Those patients with a prior hysterectomy without oophorectomy must have been at least age 50 years. Patients who had undergone therapeutic oophorectomy must have had subsequent tumor progression. Patients could not have received any prior additive hormonal therapy for breast carcinoma with estrogens, progestins, or androgens. Prior adjuvant therapy with TAM was permissible provided that at least 1 year had elapsed from discontinuation of TAM to identification of recurrent disease. Therapy with TAM at the time of entry on study was permissible provided that less than 30 days had elapsed since the initiation of TAM. Patients could not have received more than one prior chemotherapy regimen, and this could have been given only in the adjuvant setting. It was required that patients have estrogen receptor (ER) or progesterone receptor (PgR) positive tumors or that the receptor status be unknown. When hormone receptor assays had been determined on more than one occasion, the most recent were used for eligibility purposes. Patients could have disease that was measurable, evaluable, or nonevaluable. To be considered measurable, a lesion must have had clearly measurable perpendicular diameters or, in the case of hepatomegaly, a liver edge palpable 5 cm or more below a costal margin or the xiphoid, or a liver scan filling defect at least 5×5 cm. The evaluable disease designation required purely lytic bone disease or other disease that could be evaluated but did not have measurable perpendicular diameters. Bone lesions could only be considered evaluable. A nonevaluable designation required that disease be present that did not fulfill criteria for either measurable or evaluable. Examples of nonevaluable disease are malignant pleural effusion or ascites and blastic or mixed lytic/blastic osseous metastases. Patients with central nervous systemic (CNS) metastasis as the only evidence of disease were not eligible. Patients must not have had a second known primary tumor that might make the origin of metastasis questionable. The Eastern Cooperative Oncology Group (ECOG) performance score must have been 2 or better. Serum calcium must have been less than 10% above the upper limit of the institutional definition of normal (ULN) and serum total bilirubin less than 0.8 mg/dL above the ULN. This trial was performed after approval by local institutional review boards and in accordance with assurances filed with and approved by the Department of Health and Human Services (DHHS). Written informed consent was provided by each patient before entry on study.

Tests and procedures performed prior to entry on study included a history; physical examination; hema-

tologic studies, including hemoglobin, leukocyte count, and platelet count; chemistry group, including total bilirubin, serum glutamic oxaloacetic transaminase, alkaline phosphatase, calcium, and creatinine levels; total thyroxine; chest radiograph, metastatic bone survey or bone scan with radiographs of abnormal areas, and liver imaging if abnormalities of liver function or hepatomegaly were noted. When the trial first opened, patients were required to have a baseline ultrasound examination of the gallbladder, but this requirement was eliminated after 75% of the patients had been accrued. The protocol was also amended to obtain serum to study IGF-I biology after approximately one-third of patients had been entered.

Patients were stratified according to estrogen receptor (ER) and progesterone receptor (PgR) status (ER positive[+]/PgR+ or unknown vs. ER+/PgR negative[−] vs. ER− or unknown/PgR+ vs. no receptor data), ECOG performance score (0 or 1 vs. 2), dominant disease status (soft tissue vs. osseous vs. visceral), indicator lesion status (measurable vs. evaluable vs. nonevaluable), and prior adjuvant TAM (yes vs. no). Patients were then randomized to treatment with either TAM alone or TAM plus octreotide according to a dynamic allocation procedure[13] that balanced the marginal distributions of the stratification factors between treatment arms. TAM was administered orally at a dose of 10 mg twice daily. Octreotide (supplied as Sandostatin by Novartis Pharmaceuticals Corporation, East Hanover, NJ) was administered subcutaneously at a dose of 150 μg 2 times on Day 1 and thrice daily at approximately 8-hour intervals thereafter. The octreotide was self-administered by patients after instruction by the nursing staff. Patient compliance for both TAM and octreotide utilization was determined by patient interviews at the time of follow-up assessments.

After initiation of therapy, patients were to be assessed at 1 month, 2 months, every 2 months on 5 occasions, and every 3 months thereafter. Treatment was continued if the status of the patient was stable or better and if no unacceptable toxicity had occurred. At each evaluation a patient with measurable disease was classified as having a complete response (CR), a partial response (PR), stable disease (STAB), or progressive disease (PROG), where a CR was defined as the disappearance of all evidence of tumor; a PR was defined as at least a 50% reduction in the product of perpendicular diameters of the indicator lesions or at least a 30% reduction in the sum of linear measurements of the liver below both costal margins in the midclavicular lines and xiphoid, without progression of any lesion or appearance of new lesions; PROG was defined as an increase of more than 25% in the product of perpendicular diameters of indicator lesions, an increase of more than 25% in the sum of linear liver measurements, or the appearance of a new lesion; and STAB was defined as failure to quality as a CR, PR, or PROG. A patient with evaluable disease was classified as either having a CR, regression (REGR), STAB, or PROG, where a CR was the disappearance of all evidence of tumor; REGR was a definite decrease in tumor size; STAB was no definite increase or decrease in tumor size; and PROG was a definite increase in tumor size or the appearance of a new lesion. A patient with nonevaluable disease was classified at each evaluation as CR, STAB, or PROG, where CR and PROG were defined in the same manner as for evaluable patients and STAB was defined as remaining evidence of disease but no clear evidence of progression.

IGF-I, free IGF-I, and IGF BP-3 (the circulating binding protein to which >95% of circulating IGFs are bound) were measured using immunoradiometric assay (free IGF-I) or enzyme-linked immunosorbent assay (IGF-I, IGF BP-3) methods and reagents from Diagnostic Systems Laboratories, Inc. (Webster, TX).

Serum IGF BPs were analyzed by ligand blotting, as previously described.[14] Briefly, unreduced serum samples were processed by sodium dodecyl sulfate–polyacrylamide gel electrophoresis using a 7.5–15% linear gradient, and separated proteins were electroblotted onto nitrocellulose filters. Filters were blocked, labeled with [^{125}I] IGF-I overnight at 4°C, and visualized by autoradiography, according to the method of Hossenlopp et al.[15] Labeled bands were quantified using PhosphoImager SI and ImageQuaNT software (Molecular Dynamics, Sunnyvale, CA).

Eligible patients with measurable or evaluable disease were evaluable for the endpoint of objective response. A patient with measurable or evaluable disease was considered to have achieved an objective response if she maintained a CR, PR, or REGR on 2 consecutive evaluations at least 4 weeks apart. Duration of response was defined as the time from the identification of response to the time disease progression was documented.

All eligible patients were evaluable for the endpoints of progression and survival. Time to disease progression was defined as the time from randomization to the time disease progression was documented. Patients who died without documentation of disease progression were considered to have disease progression at the date of their death unless there was clear evidence at the time of death that they had not progressed. (One patient on the TAM treatment arm who died of cardiac arrest 4 days postrandomization was considered not to have progressed at the time of her death.)

TABLE 1
Patient Characteristics

	TAM	TAM plus OCT
No. of patients	68	67
Age (yrs)		
Median	65	65
Range	41–82	40–88
Menopausal status (%)		
1–5 yrs post	12	4
>5 yrs post	69	79
Prior oophorectomy	19	16
Disease free interval (%)		
<1 yr	21	30
1–5 yrs	32	36
>5 yrs	47	34
Prior adjuvant chemotherapy (%)	32	30
Prior adjuvant TAM (%)	7	7
ECOG performance score		
0	62	58
1	32	33
2	6	9
Dominant disease status		
Soft tissue	10	15
Osseous	40	48
Visceral	50	37
Indicator lesion		
Measurable	37	37
Evaluable	41	42
Nonevaluable	22	21
No. of metastatic sites		
1	38	43
2	34	37
3	21	15
4	7	3
5	0	1
Hormone receptors		
ER pos/PgR pos or unk	71	69
ER pos/PgR neg	16	19
ER neg or unk/PgR pos	1	3
No receptor data	12	9

TAM: tamoxifen; OCT: octreotide; ER: estrogen receptor; PgR: progesterone receptor; ECOG: Eastern Cooperative Oncology Group.

The Fisher exact test was used to assess whether the objective response rate differed with respect to treatment.[16] The distributions of response duration, progression free survival (PFS), and overall survival (OS) were estimated using the Kaplan–Meier method.[17] For each of these distributions, a log rank test was used to assess whether the distribution differed with respect to treatment.[18] For each of these three endpoints, a univariate Cox proportional hazards model was fit to the data to obtain an estimate of the risk of the event for the TAM plus octreotide arm relative to that for the TAM arm.[19]

The following factors were assessed for their prognostic value in terms of response duration, PFS, and OS: age (≥65 years, <65 years); menopausal status (<5 years vs. >5 years vs. prior castration); prior chemotherapy (yes vs. no); prior adjuvant therapy (yes vs. no); disease free interval (<1 year vs. 1–5 years vs. >5 years); dominant disease (soft tissue vs. osseous vs. visceral); number of metastatic sites at time of randomization; ER/PgR status (ER+/PgR+ or unknown vs. ER+/PgR− vs. ER− or unknown/PgR+ vs. no data available); ECOG performance status (0 vs. 1 vs. 2); and type of indicator lesion (measurable vs. evaluable vs. nonevaluable). For each of these factors, a univariate logistic regression model was fit to the response data to assess whether the response rates differed with respect to that factor. Multivariate logistic regression modeling was performed to obtain a subset of the potential prognostic factors that provided an adequate fit to the response data.[20] A likelihood ratio test was then performed to assess whether treatment made a significant contribution to the model. A log rank test was used to assess whether the distributions of PFS or OS differed with respect to any of the potential prognostic factors.[18] For each of these distributions, multivariate Cox proportional hazards modeling was performed to obtain a subset of the potential prognostic factors that provided an adequate fit to the data.[17] A likelihood ratio test was then performed to assess whether treatment made a significant contribution to the model.

The Wilcoxon rank sum test was used to assess 1) whether the pretreatment level of IGF-I, free IGF-I, IGF BP-3, and total IGF-I binding capacity differed between the treatment regimens, and 2) whether the percentages of change in the pretreatment levels of these 4 factors at 3–6 weeks differed between the treatment regimens. For each treatment arm, the Wilcoxon signed rank test was used to assess whether the median percentage of change in pretreatment levels of these 4 factors at 3–6 weeks differed from zero.[21]

All hypothesis tests were two-sided. A P value ≤0.05 was considered significant. A total of 150 patients per arm was to be accrued, but low accrual led to the termination of accrual.

PATIENTS

A total of 142 patients were entered on this trial between December 1989 and October 1994, and 7 patients (5%) were declared ineligible. One patient receiving TAM only was declared ineligible because she lacked documentation of PROG in a previously irradiated lesion, which was the only assessable disease. Six patients on TAM plus octreotide were declared ineligible because metastatic disease was related to a second primary rather than to breast carcinoma (3 patients), ER and PgR negative tumors (2 patients), and

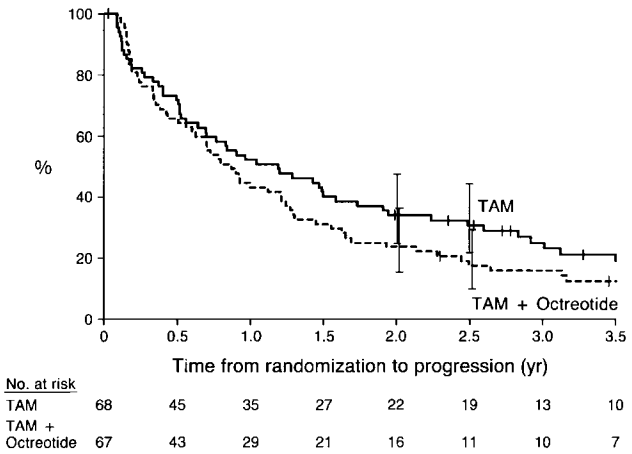

FIGURE 1. Progression free survival is shown for patients treated with tamoxifen (TAM) alone or TAM combined with octreotide. Hashed marks indicate censored patients and error bars indicate 95% confidence intervals.

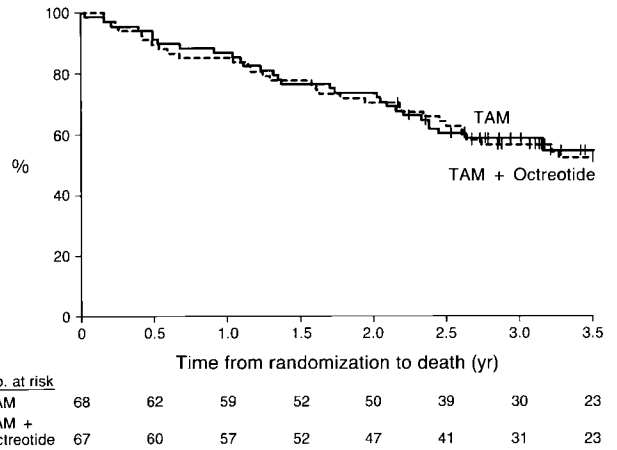

FIGURE 2. Overall survival is shown for patients treated with tamoxifen (TAM) alone or TAM combined with octreotide. Hashed marks indicate censored patients and error bars indicate 95% confidence intervals.

prior chemotherapy for metastatic disease (1 patient). The characteristics of the 135 eligible patients are given in Table 1. Among the eligible patients, those randomized to TAM had a higher proportion with visceral dominant disease and disease free interval longer than 5 years. Regarding the other baseline characteristics, the distribution of patients was well balanced between the two treatment groups.

RESULTS

Time to Disease Progression

All patients have been followed until death or for a minimum of 2.2 years. Disease progression has been noted in 115 of 135 patients. The median time to progression was estimated to be 14.2 months (95% CI: 8.2–22.8 months) for patients receiving TAM only and 10.3 months (95% CI: 7.3-15.2 months) for patients receiving TAM plus octreotide. The distribution of PFS times (Fig. 1) was not found to be significantly different between the treatment arms ($P = 0.26$). The progression hazard ratio (TAM/TAM plus octreotide) was estimated to be 0.81, with a 95% CI of 0.56–1.17. Based on an accrual period of 4.9 years, a minimum follow-up period of 2.2 years, and a median time to progression on the TAM regimen of 14.2 months, there was 84% power to detect a 75% improvement in median time to progression with the addition of octreotide to TAM (i.e., from 14.2 months to 24.8 months) with a two-sided alpha = 0.05 (log rank test). The PFS was found to be significantly increased for women with ER+/PgR+ or unknown tumors ($P = 0.01$). PFS was not found to differ univariately with respect to ECOG performance status, length of disease free interval, prior chemotherapy, prior TAM, dominant disease status, type of indicator lesion, number of metastatic sites, or menopausal status. Multivariate Cox regression analysis indicated that PFS was significantly increased for those women who were receptor status ER+/PgR+ or unknown relative to those patients with other receptor status. After adjustment for this variable, PFS was not found to differ significantly with respect to treatment regimen ($P = 0.26$). The adjusted progression hazard ratio (TAM/TAM plus octreotide) was estimated to be 0.81, with a 95% CI of 0.56–1.17.

Survival

Seventy-three of the 135 eligible patients have died. The 3-year survival rate was estimated to be 58% (95% CI: 48–72%) for patients receiving TAM and 56% (95% CI: 45–70%) for patients receiving TAM plus octreotide. The distribution of survival times (Fig. 2) was not found to differ significantly between the treatment groups ($P = 0.92$). The death hazard ratio (TAM/TAM plus octreotide) was estimated to be 0.98 with a 95% CI of 0.62–1.55. Based on an accrual period of 4.9 years, a minimum follow-up period of 2.2 years, and a median survival time on the TAM regimen of 4.4 years, there was 82% power to detect a 120% improvement in the median survival time with the TAM plus octreotide regimen (i.e., from 4.4 years to 9.7 years) with a two-sided alpha = 0.05 log rank test.

Univariate analysis indicated that the survival significantly increased for women with ER+/PgR+ or PgR-unknown tumors ($P = 0.04$), women with at most 2 metastatic sites ($P < 0.01$), and women whose performance score was 0 ($P = 0.02$). Survival was not found to differ univariately with respect to either length of disease free interval, prior chemotherapy,

prior TAM, type of dominant disease, type of indicator lesion, or menopausal status. Multivariate Cox regression analysis indicated that survival was significantly increased for women who had an ECOG performance score of 0 and at most 2 metastatic disease sites. After adjustment for these variables, OS was not found to differ significantly with respect to treatment regimen ($P = 0.89$). The adjusted death hazard ratio (TAM/TAM plus octreotide) was estimated to be 0.89 with a 95% CI of 0.56–1.41.

Response Data

One hundred six patients with measurable or evaluable disease were assessable for objective response (Table 2). The overall objective response rate for patients receiving TAM alone was 49% (95% CI: 35–63%) and for patients receiving TAM plus octreotide 43% (95% CI: 30–58%). The overall objective response rates were not found to differ significantly between the two treatment regimens ($P = 0.70$). The 95% CI for the difference in objective response rates between TAM and TAM plus octreotide was −13% to +25%.

Univariate analysis indicated that those more likely to respond to treatment were women with soft tissue dominant disease ($P = 0.03$), women who were postmenopausal for at least 5 years at the time of study entry ($P = 0.03$), and women with ER+/PgR+ or unknown tumors ($P = 0.03$). The objective response rate was not found to differ univariately in terms of age at randomization, number of metastatic sites, length of disease free interval, type of indicator lesion, ECOG performance score, prior adjuvant therapy with TAM, or prior chemotherapy. Multivariate logistic regression analysis indicated that the likelihood of attaining an objective response was increased for women who had soft tissue dominant disease, were postmenopausal for at least 5 years at the time of initiation of treatment, and had ER+/PgR+ or unknown tumors. After adjusting for these factors, the objective response rates were not found to differ significantly between the treatment regimens ($P = 0.35$).

The response durations for the 49 patients who achieved an objective response are given in Figure 3. The estimated probability that the duration of response was less than 1 year was 69% for TAM and 78% for TAM plus octreotide. The duration of response was not found to differ significantly between the treatment regimens ($P = 0.56$).

Toxicity

The toxicities identified for the two treatment arms are given in Table 3. Patients receiving TAM plus octreotide had a higher incidence of nausea, diarrhea, and steatorrhea. Twenty-one percent of patients receiving octreotide reported pain at the injection site. Two patients, both on TAM plus octreotide, experienced a phlebitis.

Seven patients discontinued octreotide because of gastrointestinal complaints (i.e., bloating, gas, and diarrhea) in 4 cases, weight loss and anorexia in 1 case, severe hot flushes in 1 case, and refusal in 1 case. Three patients reduced octreotide because of diarrhea in 2 cases and musculoskeletal pain in 1 case. Three patients were noncompliant. Two additional patients briefly interrupted their octreotide administration for several weeks for personal reasons (i.e., a trip or a family illness) but restarted the agent. Thus, 15 of the 67 patients (22%) receiving TAM plus octreotide reduced, stopped, or were noncompliant with the octreotide regimen.

TABLE 2
Objective Response Rate Achieved among Patients with Measurable or Evaluable Disease

Indicator lesion	TAM (%)	TAM plus OCT
Measurable	n = 25	n = 25
CR	4 (16)	4 (16)
PR	7 (28)	9 (36)
CR + PR	11 (44)	13 (52)
Evaluable	n = 28	n = 28
CR	4 (14)	3 (11)
REGR	11 (39)	7 (25)
CR + REGR	15 (54)	10 (36)
ORR (CR + PR + REGR)	26/53 (49)	23/53 (43)
95% CI for ORR	35–63%	30–58%

TAM: tamoxifen; OCT: octreotide; CR: complete response; PR: partial response; REGR: regression; ORR: objective response rate; CI: confidence interval.

Insulin-Like Growth Factor Analyses

There were 18 patients (10%) (10 on TAM, 8 on TAM + octreotide) who had serum available for analysis from both the pretreatment period and a 3- to 6-week window following the start of treatment. IGF-I, free IGF-I, IGF BP-3 levels, and total IGF-I binding capacity were determined, and the pretreatment levels were not found to differ significantly between the treatment regimens. On the TAM arm, the percent decline in free IGF-I from pretreatment levels was significant ($P = 0.03$), whereas the IGF-I levels decreased from pretreatment levels but failed to reach statistical significance. On the TAM + octreotide arm, the percentage of decline in IGF-I from treatment levels was significant ($P < 0.01$), whereas the free IGF-I levels decreased from pretreatment levels but failed to reach statistical significance. The percentage of change in IGF BP-3 and total IGF binding capacity was not found to be significant on either treatment arm. The percent-

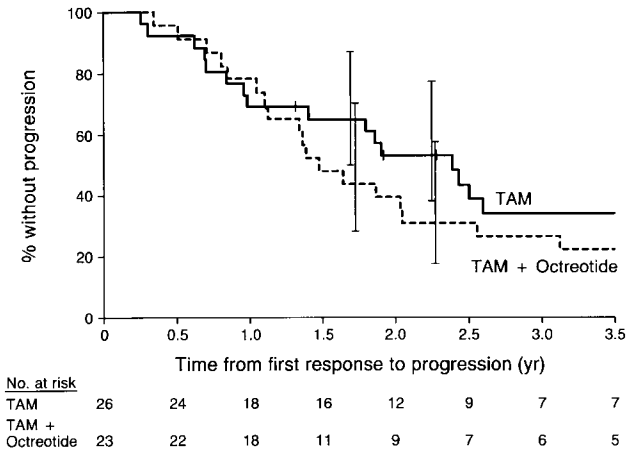

FIGURE 3. Duration of response is shown for patients treated with tamoxifen (TAM) alone or TAM combined with octreotide. Hashed marks indicate censored patients and error bars indicate 95% confidence intervals.

age of decline in IGF-I levels was significantly greater ($P < 0.01$) on the TAM + octreotide arm than on the TAM arm (median percentage of change, −38.9% and −16.5%, respectively) (Fig. 4). The percentage of change in free IGF ($P = 0.27$), IGF BP-3 levels ($P = 0.57$), and total IGF-I binding capacity ($P = 0.90$) were not found to differ between the treatment arms.

DISCUSSION

The endpoint of primary interest in this trial was time to disease progression, as we had hypothesized that octreotide would have antiproliferative or cytostatic effects. There was no significant difference in time to progression between TAM alone and TAM plus octreotide. The progression hazard ratio (TAM/TAM plus octreotide) of 0.81 favored TAM alone, but the study was sufficiently powered to only rule out a 75% improvement in median time to progression with the addition of octreotide to TAM. In terms of survival for all patients and objective response rate for patients with measurable or evaluable disease, there was no significant difference between the two regimens and no suggestion that TAM plus octreotide was superior.

There has been a substantial increase in knowledge relating to somatostatin analogues[22] and the rationale for combining antiestrogens and somatostatin analogues[23] in the decade since this trial was developed. In a preclinical nonacromegalic rat model, the combination of TAM plus octreotide produced a significantly greater reduction in serum IGF-I concentration and hepatic IGF-I gene expression than either TAM or octreotide alone.[24] Weckbecker et al.[25] evaluated the efficacy of TAM, octreotide, and the combination in 7,12-dimethylbenz(a)anthracene (DMBA)–induced rat mammary carcinomas. These agents were started 7 weeks after DMBA administration, which is about 1 week before the appearance of tumors that could be considered analogous to the adjuvant therapy setting in humans. The number and volumes of

TABLE 3
Maximum Toxicity Observed

	TAM (n = 68)	TAM plus OCT (n = 67)
	%	%
Nausea		
Any	10	33
≥Grade 3[a]	0	3
Emesis		
Any	7	9
≥Grade 3	0	1
Diarrhea		
Any	3	30
≥Grade 3	0	6
Steatorrhea		
Any	4	9
≥Grade 3	0	0
Abdominal pain/bloating		
Any	0	3
≥Grade 3	0	1
Constipation		
Any	1	3
≥Grade 3	0	0
Anorexia		
Any	9	10
≥Grade 3	0	0
Lethargy		
Any	4	9
≥Grade 3	0	1
Neurologic mood		
Any	3	3
≥Grade 3	0	1
Alopecia		
Any	0	6
≥Grade 3	0	0
Edema		
Any	10	7
≥Grade 3	0	0
Hot flashes		
Any	51	45
≥Grade 3	6	1
Vaginal bleeding		
Any	4	3
≥Grade 3	0	0
Vaginal discharge		
Any	6	6
≥Grade 3	0	1
Leg cramps		
Any	0	1
≥Grade 3	0	1
Pain at injection site		
Any	—	21
≥Grade 3	—	0

TAM: tamoxifen; OCT: octreotide.
[a] By Common Toxicity Criteria.

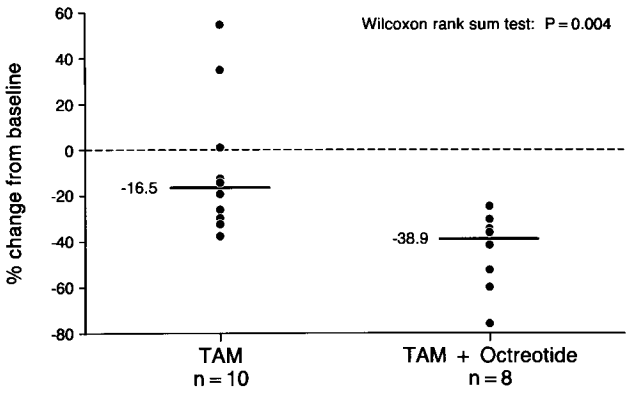

FIGURE 4. Percentages of change in insulin-like growth factor-I levels, from pretreatment to following 3–6 weeks of therapy, are shown according to treatment arm. TAM: tamoxifen.

tumors per animal were significantly less with the combination of TAM plus octreotide than with either agent alone. Pollak[26] has noted that, in all experimental systems, the response to octreotide is greater in smaller than in larger tumors. This raises the possibility that a combined antiestrogen-octreotide regimen might be more appropriately studied in the adjuvant setting.

We hypothesized that serum IGF-I levels would be reduced to a greater extent with TAM plus octreotide than with TAM alone. In a small cohort of 18 patients, this was found to be the case, with the percentage in decline from pretreatment levels to levels after 3–6 weeks of treatment being significantly greater with TAM plus octreotide. This was not found to be the case for free IGF-I, IGF BP-3, or total IGF-I binding capacity. The finding of a significant reduction in IGF-I levels in the patients receiving TAM plus octreotide supports the impression that patients were reliable in their self-reporting of octreotide administration. The small sample size and multiple testing indicates that caution should be employed in interpreting the results.

In conclusion, we could find no indication that the combination of TAM and octreotide as given in this study was superior to TAM alone in terms of time to disease progression in postmenopausal women with metastatic breast carcinoma. Of note is that a depot form of octreotide has been developed which produces more sustained levels.[27] However, it remains to be seen whether this depot form of octreotide will be of value in combination with TAM, and this question is currently being addressed by a clinical trial of metastatic breast carcinoma. In addition, preclinical data suggest that the antiestrogen plus somatostatin analogue approach may be more effective in the adjuvant setting than in the setting of metastatic disease and clinical trials of the combination as adjuvant therapy are in progress.

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