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Treatment of Metastatic Breast Cancer With Somatostatin Analogues—A Meta-Analysis

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Background: Somatostatin analogues appear to have antiproliferative effects in breast cancer by inhibiting various hormones. Several small phase 1 and 2 clinical trails have evaluated the efficacy of somatostatin analogues, but the results are varied. The purpose of this study was to use the technique of meta-analysis to determine the effect of somatostatin analogues on tumor response, toxicity, and serum hormone levels in women with metastatic breast cancer.

Methods: All published and unpublished trials were reviewed. Meta-analysis was preformed by best linear unbiased estimate regression with observations weighted inversely to their variance. Significance was considered at $P < .05$.

Results: Fourteen studies (N = 210) were included. Positive tumor response was reported in 87 patients (41.4%). Mean duration of response was 3.9 months. Response was best when somatostatin analogues were given as first-line therapy (69.5% versus 28.5%, $P < .006$) and in patients with ≤2 metastases (45.0% versus 5.6%, $P = .3$). Mild side effects occurred in 47 of 185 patients (25.4%). Therapy was associated with a decrease in serum insulin-like growth factor (IGF-1) and an increase in growth hormone.

Conclusions: In patients with metastatic breast cancer, treatment with somatostatin analogues was associated with a tumor response of over 40% with few side effects. Best results were achieved when somatostatin analogues were given as first-line therapy.

Key Words: Breast cancer—Somatostatin—Octreotide—Somatuline—Lanreotide—Treatment—Outcomes—Meta-analysis.

Breast cancer remains the most common cancer diagnosed in women in the United States. Approximately one third of all breast cancers are hormone-dependent, and much effort has been directed at understanding and manipulating hormones in an effort to treat primary and metastatic disease. Estrogens, most notably estradiol, and insulin-like growth factor (IGF-1) are among the most potent stimulators of breast cancer cells. Both hormones work via IGF-1 receptors. Growth hormone (GH) stimulates IGF-1 secretion. Somatostatin, a regulatory-inhibitory peptide hormone, suppresses both IGF-1 and GH secretion. Numerous investigators have demonstrated the antiproliferative effects of somatostatin and its analogues on breast cancer, both in vitro and in vivo.[1] In animal models, treatment with somatostatin analogues resulted in a significant decrease tumor growth.[2]

In the past decade, somatostatin analogues, alone or in combination with other agents, have been studied in phase 1 and 2 clinical trials as a treatment for women with metastatic breast cancer. These studies have produced varied results, and the small number of patients in each study makes it difficult to draw conclusions. Meta-analysis can be used to combine the results of these small, homogeneous prospective clinical trials and draw more reliable conclusions. Results of meta-analysis can then be used to help plan prospective phase 3 clinical trials.

The purpose of this paper was to review all available published and unpublished clinical trials in which somatostatin analogues were used to treat women with metastatic breast cancer, and to use the technique of meta-

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analysis to determine its toxicity, tumor response, and effect on serum levels of IGF-1 and GH.

METHODS

The world literature in all languages between 1989 and 1998, inclusive, was searched. Several techniques were used to identify all clinical trials using somatostatin analogues in breast cancer, both published and unpublished. Unpublished data were included because they may have contained negative results and therefore never been published ("publication bias"). An electronic search of the world literature using the key words "somatostatin" and "breast cancer" was performed, and all articles related to the topic were retrieved. Then a systematic, manual secondary search of the bibliographies of these first papers was performed and articles were retrieved. The bibliographies from the secondary survey were again reviewed, and so on, until it became clear that we had every article published on this topic. Abstracts of the annual meetings of the American Society of Clinical Oncology and the American Association for Cancer Research between 1989 and 1998 were reviewed. Breast cancer experts were contacted and asked if they were aware of any other research in the area. The Cochrane Controlled Trials register, an electronic on-line service that gathers clinical trials on various topics, was reviewed.[3] Care was taken to review the papers closely to be sure that the same patients were not reported more than once. All of the papers reviewed were kept in a database. Criteria for inclusion in the meta-analysis were as follows: (1) the studies used human subjects with metastatic breast cancer treated with a somatostatin analogue; (2) the type and dose of somatostatin analogue used was provided; and (3) response to treatment was reported. All of the papers that met the inclusion criteria were recorded in a second database.

Each study used in the meta-analysis was reviewed independently by the first and second authors using a standardized record form. Their results were compared, and any differences were reconciled. These data were then entered on a spreadsheet (Microsoft Excel 97, Microsoft Corp., Redmond, WA). Primary data points were drug formulation, drug regimen, and response to therapy.

The drug formulations used were octreotide or lanreotide (Somatuline), in a long-acting depo (injectable) formulation. According to the manufacturer, doses of these somatostatin analogues were considered equivalent with regard to biological activity. Both drugs were available during the time frame.

Dosing regimens varied greatly across studies, so patients were grouped for purposes of data analysis. Daily doses of somatostatin analogues ranged from 0.2 mg/day to 9.8 mg/day (mean, 1.8 mg/day). Patients were arbitrarily grouped as receiving $>$ or $\leq$2 mg/day. The total amount of somatostatin analogue received ranged from 2.8 mg to 2.6 g (mean, 200 mg). Patients were arbitrarily grouped as receiving $>$ or $\leq$200 mg total dose of somatostatin analogue. Length of treatment ranged from 2 weeks to 72 months, with an average of 4 months. Patients were grouped as receiving treatment for $>$ or $\leq$4 months.

Women with metastatic cancer were considered to have a positive tumor response if they had any of the following: complete response, defined as complete disappearance of all known disease; partial response, defined as $>$50% decrease in known lesions with no appearance of new lesions; or stabilization of disease, defined as $<$25% increase or $<$50% decrease in known lesions. A negative tumor response was defined as an increase in disease greater than 25%. Other data were extracted when available, including menopausal status, number and location of metastasis, other hormonal therapy administered, duration of response, toxicity, patient dropout rate, and effect of somatostatin analogues on IGF-1, GH, and prolactin.

Two types of analysis were performed. In the first analysis, data on patient features (menopausal status, number and site of metastases) and outcome (tumor response, duration of response, toxicity and number of dropouts, effect on IGF-1 and prolactin) from each individual study were pooled. The second analysis was a meta-analysis, in which the effect of somatostatin analogue formula, daily dose, total dose, length of treatment, and hormone combination on tumor response was calculated. Data sets were summarized, verified, and entered by the authors into a spreadsheet database for storage. The five treatment factors were treated as bivariant covariables. χ^2 statistics and Fisher's exact test (when sample size was small) were conducted on the cumulative data. Summarized data were then compared by best linear unbiased estimate regression, with observations weighted inversely to their variance. Significance was considered as $P < .05$.

RESULTS

Seventeen clinical trials were identified, and 14 trials including a total of 210 subjects met the inclusion criteria (Table 1).[4–16] Nine of the trials were conducted in Europe; five were from North America. The mean number of patients enrolled in each study was 15 (range, 6 to 32).

TABLE 1. *Clinical trials*

Author	No. patients	Country
Vennin et al., 1989[4]	14	France
Morere et al., 1989[5]	30	France
Manni et al., 1989[6]	9	USA
Stolfi et al., 1990[7]	10	Italy
Cannata et al., 1992[8]	30	Italy
Pollak et al., 1992[9]	11	Canada
Pollak et al., 1992[9]	7	Canada
Somlo et al., 1993[10]	20	USA
Bonneterre et al., 1993[11]	13	France
Anderson et al., 1993[12]	6	United Kingdom
Canobbio et al., 1995[13]	32	Italy
DiLeo et al., 1995[14]	10	Italy
Ingle et al., 1996[15]	9	USA
Bontenbal et al., 1998[16]	9	Netherlands
Total	210	

Patient Characteristics

Menopausal status was reported in nine studies (n = 193). The vast majority of patients were postmenopausal (95.0%). Nine studies (n = 156) gave details about metastasis. The mean number of metastatic sites per patient was 1.7. Metastasis involved soft tissue sites (contralateral breast, lymph nodes, and skin) in 62.5%, bone in 21.0%, and solid viscera (lung, liver) in 16.4% of cases.

Tumor Response

Overall

A positive tumor response was reported in 87 patients (41.4%) (Tables 2 and 3). There was a complete response in 9 patients (4.3%), partial response in 31 patients (14.8%), and stabilization of disease in 47 patients (22.4%). Duration of response was reported in 72 patients: the mean duration of response was 3.9 months (range, 1.6 to 9 months).

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Drug Formula

Octreotide was used in nine trials (n = 95) and lanreotide was used in five trials (n = 115). The positive tumor response for octreotide and lanreotide, alone or in combination with other hormones, was 28.4% and 52.2%, respectively. Somatostatin analogues were used alone in seven studies (n = 104) and in combination with other hormones in seven studies (n = 106). The positive tumor response for somatostatin analogues is 37.9% when used alone and 62.1% when used in combination with other hormones. Although it appears that lanreotide in combination with other hormones is the most efficacious formula, when meta-analysis is applied, there was no statistically significant difference in tumor response, no matter which somatostatin analogue was used or whether analogues were used alone or in combination with other hormones.

Daily Dose

All studies reported the daily dose of somatostatin analogue. Dosage interval varied from once a day to three times a day. Patients were given ≤ 2 mg somatostatin analogue per day in six studies (n = 115) and >2 mg/day in eight studies (n = 95). A positive tumor response was seen in 42.5% of patients who received ≤ 2 mg/day compared to 57.5% in those who received >2

TABLE 2. *Treatment regimen*

Author	No. patients	Hormone formulation	Hormone therapy given first	Mean daily dose		Mean total dose		Mean treatment time	
				≤2 mg/d	>2 mg/d	≤200 mg	>200 mg	≤4 mos.	>4 mos.
Vennin et al., 1989[4]	14	OCT[a]	Yes	+		+		+	
Morere et al., 1989[5]	30	SOM[b] + TAM	Yes	+			+		+
Manni, et al., 1989[6]	9	OCT[a] + BROMO	Yes	+		+			+
Stolfi et al., 1990[7]	10	OCT[c]	Mixed*		+	+		+	
Cannata et al., 1992[8]	30	SOM[d] + TAM	No		+		+		+
Pollak et al., 1992[9]	11	OCT[d]	Yes	+		Not stated		Not stated	
Pollak et al., 1992[9]	7	OCT[d] + CV	Yes	+		Not stated		Not stated	
Somlo et al., 1993[10]	20	OCT[d]	Yes		+		+		+
Bonneterre et al., 1993[11]	13	SOM[d] + BROMO	Yes		+	Not stated		Not stated	
Anderson et al., 1993[12]	6	OCT[d] + BROMO	Yes	+		Not stated		Not stated	
Canobbio et al., 1995[13]	32	SOM[b] + TAM	No		+		+	+	
DiLeo et al., 1995[14]	10	SOM[b]	Mixed*		+	Not stated		Not stated	
Ingle et al., 1996[15]	9	OCT[a]	Mixed*	+		+			+
Bontenbal et al., 1998[16]	9	OCT[a] + TAM + CV	No	+			+		+

BROMO, bromocriptine; CV, CV205-502; OCT, Octreotide; SOM, Somatuline; TAM, Tamoxifen.
* Either hormone therapy was given as the initial therapy for metastases, or another therapy was given first, followed by hormone therapy.
[a]Sandoz; [b]Ipsen; [c]Serono; [d]Not stated.

TABLE 3. *Outcome*

Author	No. patients	Mean number of metastases		Response to treatment	
		≤2	>2	Positive	Disease progression
Vennin et al., 1989[4]	14	+		3	11
Morere et al., 1989[5]	30	+		15	15
Manni et al., 1989[6]	9		+	1	8
Stolfi et al., 1990[7]	10	Not stated		3	7
Cannata et al., 1992[8]	30	+		12	18
Pollak et al., 1992[9]	11	Not stated		8	3
Pollak et al., 1992[9]	7	Not stated		1	6
Somlo et al., 1993[10]	20	Not stated		2	18
Bonneterre et al., 1993[11]	13	Not stated		2	11
Anderson et al., 1993[12]	6	Not stated		2	4
Canobbio et al., 1995[13]	32	+		29	3
DiLeo et al., 1995[14]	10	+		2	8
Ingle et al., 1996[15]	9		+	0	9
Bontenbal et al., 1998[16]	9	+		7	2

mg/day, but this difference was not statistically significant.

Total Dose

Total dose was reported in nine studies. In four studies (n = 42), ≤200 mg total dose was given; in five studies (n = 121), >200 mg was given. Of the patients who were given a total dose >200 mg, 53.7% had a positive tumor response, compared to only 16.6% in those who received ≤200 mg. Although this difference did not reach statistical significance, there was a trend for women receiving a higher total somatostatin dose to have a positive tumor response compared to those receiving a lower total dose ($P = .06$).

Length of Treatment

Length of treatment was reported in nine studies. In three studies (n = 56) somatostatin analogue was given for ≤4 months; in the other six studies (n = 107) it was given for >4 months. A positive response was seen in 62.5% of those who had short treatment compared to 34.6% in those who had long-term treatment (P = NS).

Timing

Eleven studies (n = 181) reported the timing of treatment with somatostatin analogues with regard to other agents. Somatostatin analogues were used as initial treatment for metastasis in 71 patients, whereas other chemotherapeutic or hormonal treatments were administered first, followed by a somatostatin analogue, in 110 patients. When somatostatin analogues were given as first-line therapy, 69.5% of patients showed a positive tumor response, compared to 28.5% in those who received other therapies first ($P < .006$).

Number of Metastatic Sites

Nine studies (n = 156) provided details about metastatic burden. Forty-five percent of patients with only one or two metastatic sites had a positive tumor response, compared to 5.6% of patients with more than two metastatic sites ($P = .3$).

Toxicity and Dropout Rate

Specific side effects were reported in 11 studies (n = 185); the incidence was 25.4%. Nausea and vomiting occurred in 5.9% of patients, abdominal pain or cramping occurred in 8.6% of patients, and diarrhea was reported in 10.8% of patients. Other side effects included transient increased bone pain (6 patients), vaginal itching (5 patients), hot flashes (4 patients), vaginal bleeding (1 patient), vertigo (1 patient), constipation (1 patient), and asymptomatic gallstones (1 patient). All side effects resolved once treatment was discontinued. In three patients, somatostatin analogues were discontinued because of severe side effects: one patient each had diarrhea, nausea, and pain at the injection site.

Hormonal Response

Serum levels of insulin-like growth factor-1 (IGF-1) were measured in some patients (n = 89) in seven studies.[4,8,9,11,13,14,16] In one study,[4] four patients did not have hormone levels measured because their disease progressed rapidly and they died. In three other studies,[8,11,13] hormone levels were not measured in all patients for unspecified reasons. Administration of somatostatin analogues was associated with a decrease in serum IGF-1 in 72.7% of women. In four of these studies[9,13,14,16] (n = 52), change in IGF-1 was measured 4 to 24 weeks after starting treatment with somatostatin ana-

logues. Serum IGF-1 decreased 33.2% when compared to baseline. Serum prolactin levels were measured in three studies[6,12,16] (n = 39). In all of these patients, bromocriptine[6,12] or the prolactin suppressor CV205–502[16] was given in combination with somatostatin analogue. Serum prolactin levels decreased in 87.0% of women. In one study[16] (n = 7), prolactin levels were measured 4 to 24 weeks after starting therapy. The mean drop in prolactin was 43.8%. Serum growth hormone levels were monitored in three studies[13,14,16] (n = 33). Somatostatin analogue administration was associated with a mean serum growth hormone increase of 44.9% when measured 4 to 24 weeks after starting therapy.

DISCUSSION

Approximately one third of all breast cancers are estrogen-dependent, and the mainstay endocrine therapy of breast cancer has been the antiestrogen tamoxifen.[17] However, growth factors such as IGF-1 and various peptide hormones, including prolactin and GH, also appear to be involved in the growth and malignant transformation of breast cancer cells.[17] IGF-1 is a potent mitogen for human breast cancer cells, and its effect appears to be mediated via IGF-1 receptors, which are present in 67% to 93% of primary human breast cancers.[18] In physiological concentrations, GH and prolactin can stimulate the growth of breast cancer cells, and receptors for these hormones have been demonstrated in up to 72% of breast cancer tumors.[19] Increased plasma levels of GH,[20] prolactin,[20] and IGF-1[21] have been found in patients with breast cancer. GH up-regulates the expression of IGF-1.[22] Interestingly, tamoxifen also appears to modify GH secretion, suppress the GH/IGF-1 axis, and suppress prolactin secretion.[16] It is, therefore, hypothesized that suppression of GH, prolactin, and IGF-1 might be an effective treatment for breast cancer. Somatostatin and its analogues have been shown to suppress GH and IGF-1.[2] Somatostatin analogues also directly inhibit cancer growth through the action of specific cell surface receptors,[23] and the endogenous production of somatostatin by breast cancer cells[24] suggests that there may also be a paracrine axis for somatostatin in the breast.[25] The presence of somatostatin receptors in human breast cancers has been correlated with well-differentiated tumors and a positive prognosis.[26] There are five somatostatin receptor subtypes, and all five have been identified in human breast tumors.[27–30] Somatostatin receptor subtype 2 occurs most frequently and appears to be regulated by estrogen responsiveness in breast cancer cells.[31] Receptor subtype 5 has the greatest efficacy in inducing cell cycle arrest.[32,33]

Results of stage 1 and 2 clinical trials using somatostatin analogues to treat metastatic breast cancer have demonstrated varying results. This may be because the average number of patients in each trial is only about 15–and it is difficult to reach statistical significance with such a small sample size.

We hypothesized that somatostatin analogues were an effective treatment for breast cancer, possibly through the modulation of growth factors. We performed an exhaustive review of all available clinical trials, both published and unpublished, and applied the statistical technique of meta-analysis to determine if somatostatin analogues were associated with a positive tumor response, and if so, which treatment regimen was most efficacious.

Meta-analysis cannot be used to solve every problem, but it is well suited to this one because there are a few well-defined specific outcomes, the primary literature is of relatively good quality, and the heterogeneity in the results is small and well understood. Meta-analysis is not simply the arithmetic average of the results from all the trials. Rather, it uses a weighted average of the results, in which the larger trials have more influence than the smaller ones because small studies are more subject to chance. The technique of meta-analysis has several applications: in this instance, it is used to determine whether somatostatin has any role in the treatment of metastatic breast cancer. If the answer is yes, then a prospective randomized trial can be designed based on the details found in this meta-analysis, such as drug regimen. In the past, in order to reach a consensus, particularly a controversial one, a review of the literature was performed and an expert in the field gave an opinion, which, although based in the literature, was not always scientific. Meta-analysis is a more objective and reproducible form of review. It has been described as providing the highest level of evidence of treatment efficacy. Its results are most robust when prospective, randomized trials are used, as in this study. The random effects model was used in this analysis. It assumes a different underlying effect for each study and takes this into consideration as an additional source of variation, which leads to somewhat wider confidence intervals than the fixed effects model. The random effects analysis is generally preferred, and a National Research Council panel recently recommended that random effects analysis be used as the default statistical technique in meta-analysis.[34]

None of the studies included in this meta-analysis reported the presence or absence of somatostatin receptors in the tumors prior to beginning treatment, and only a few provided information on estrogen receptor status.

Several techniques are available for demonstrating the presence or absence of somatostatin receptors in human breast tumors, including reverse transcriptase-polymerase chain reaction (RT-PCR), in situ hybridization,[27–30] and mammographic scintigraphy.[35] It appears that the later correlates best with the identification of somatostatin-positive breast cancers when compared to receptor assay of breast biopsy,[36] suggesting that nuclear medicine may be useful in determining which women are likely to benefit from treatment with somatostatin analogues.[37] It would be useful to correlate somatostatin receptor status and response to somatostatin analogue, and further investigation in this area is warranted.

Meta-analysis demonstrated a positive tumor response in 41% of women treated with somatostatin analogues for metastatic breast cancer, but the mean duration of response was short, only 3.9 months. Median duration of response and range of duration of response could not be determined. Tumor response was best if somatostatin analogues were given as initial therapy for metastatic disease. Not surprisingly, women with two or less metastatic sites appeared to have a better tumor response than did those with a larger tumor burden. It appeared that tumor response was better when the total dose of somatostatin analogue exceeded 200 mg. Four months appeared to be an adequate length of treatment, because taking somatostatin analogues for more than four months was not associated with an improved tumor response rate. Octreotide was equally as effective as lanreotide, and tumor response did not appear to be influenced by the addition of other hormones or chemotherapy. Tumor response rate was improved when the dose of somatostatin analogue was more than 2 mg per day. The ideal daily dose of somatostatin analogue has yet to be determined. One quarter of the patients reported side effects. These usually were mild and resolved when treatment was discontinued. Two percent of patients had to stop treatment with somatostatin analogues because of severe side effects. This is important because quality of life is paramount in patients with a limited life expectancy.

Somatostatin analogues, either octreotide or lanreotide, 2 mg per day for 4 months, may be considered as initial treatment in women with breast cancer who develop metastatic disease. The mechanism of action appears to involve reduction in serum IGF-1. Further studies are needed to determine which patients are more likely to respond (such as those with tumors that express somatostatin receptors) and the role of combination therapy (somatostatin analogue plus tamoxifen plus an anti-prolactin).

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