Treatment of metastatic breast cancer with somatostatin analogues: a meta-analysis
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Authors' objectives
To determine the effect of somatostatin analogues on tumour response, toxicity, and serum hormone levels in women with metastatic breast cancer.

Searching
The literature was searched between 1989 and 1998 using the keywords 'somatostatin' and 'breast cancer', and the bibliographies of all retrieved studies were reviewed. The bibliographies of the studies subsequently identified were also searched, and the process was repeated until no further studies were identified. Additional unpublished and published material were obtained by reviewing the abstracts of the annual meetings of the American Society of Clinical Oncology and the American Association for Cancer Research between 1989 and 1998, by contacting experts in breast cancer, and by searching the Cochrane Controlled Trials Register. No language restrictions were reported.

Study selection
Study designs of evaluations included in the review
All published and unpublished trials were eligible for inclusion. The design of the included studies was not specified.

Specific interventions included in the review
Studies that examined the use of somatostatin analogues were eligible if details of the type and dose of the somatostatin analogue used were provided. The actual drugs included were octreotide and lanreotide (somatuline) in a long-acting formulation. These were used either alone or in combination with one or more of the following hormones: bromocriptine, CV205-502 and tamoxifen. The dosing regimens varied greatly across the studies: the daily dose of somatostatin analogues ranged from 0.2 to 9.8 mg/day (mean 1.8), whilst the total dose per patient ranged from 2.8 mg to 2.6 g (mean 200 mg). The duration of the treatment ranged from 2 weeks to 72 months (mean 4 months).

Participants included in the review
Women with metastatic breast cancer were eligible for inclusion. The majority (95%) of the patients were postmenopausal. The mean number of metastatic sites per patient was 1.7. The most commonly involved sites were soft tissues (62.5%), bone (21%) and solid viscera (16.4%).

Outcomes assessed in the review
Studies that reported the response to treatment were eligible for inclusion. A positive tumour response was considered to be any of the following:

- a complete response, defined as complete disappearance of all known disease;
- a partial response, defined as a greater than 50% decrease in known lesions with no appearance of new lesions; or
- stabilisation, defined as a less than 25% increase or less than 50% decrease in known lesions.

A negative tumour response was defined as an increase in disease of greater than 25%. Toxicity, drop-outs, and the effect of somatostatin analogues on insulin-like growth factor, growth hormones and prolactin levels, were also assessed.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.
Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

The following data were extracted: author and year of publication; sample size; country; intervention details; menopausal status; the number and location of metastases; other hormonal therapy; the duration of response; and the patient drop-out rate. Care was taken to ensure that the same patients were not reported more than once.

Methods of synthesis
How were the studies combined?
Data on the patients' characteristics, and the outcome from each individual study, were arithmetically pooled. In addition, a meta-analysis was conducted using a random-effects model.

How were differences between studies investigated?
The influence on the results of the following variables was explored:

- the somatostatin analogue formulation;
- the daily dose of somatostatin analogue, i.e. less than or equal to 2 mg/day versus greater than 2 mg/day;
- the total drug dose, i.e. less than or equal to 200 mg versus greater than 200 mg; and
- the duration of the treatment, i.e. less than or equal to 4 months versus greater than 4 months.

These groupings were determined arbitrarily. The five treatment factors were treated as bivariant co-variables. Chi-squared statistics and Fisher's exact test (for small sample sizes) were conducted on the cumulative data. The summarised data were then compared using a best linear unbiased estimate regression, with observations weighted inversely to their variance. A p-value of less than 0.05 was considered significant.

Results of the review
Fourteen studies (210 women) were included.

Sample size ranged from 6 to 32 patients (mean 15 patients). A positive tumour response was reported in 87 patients (41.4%). There was complete response in 9 patients (4.3%), partial response in 31 patients (14.8%), and stabilisation of disease in 47 patients (22.4%). The duration of response in 72 patients ranged from 1.6 to 9 months (mean 3.9).

Response according to drug therapy.

There was no statistically-significant difference in tumour response between different somatostatin analogues, between somatostatin analogues alone, or between combinations of somatostatin analogues plus other hormones. The response rate for analogues, either alone or in combination, was 28.4% for octreotide (9 studies, 95 patients) and 52.2% for lanreotide (5 studies, 115 patients). The response rate was 37.9% for somatostatin alone (7 studies, 104 patients), and 62.1% for somatostatin in combination with other hormones (7 studies, 106 patients).

Response according to daily dose.

There was no statistically-significant difference in tumour response between the patients who received 2 mg or less per day (6 studies, 115 patients) and those who received more than 2 mg/day (8 studies, 95 patients). The response rates were 42.5 and 57.5%, respectively.
Response according to total dose.

There was a non statistically-significant difference in tumour response rate between women receiving a higher total somatostatin analogue dose and those receiving a lower total dose (p=0.06). The response rate was 16.6% for a total drug dose of less than or equal to 200 mg (4 studies, 42 patient), compared with 53.7% for a total dose of greater than 200 mg (5 studies, 121 patients).

Length of treatment.

There was no statistically-significant difference in tumour response according to the length of treatment. The response rate was 62.5% for a treatment duration of less than or equal to 4 months (3 studies, 56 patients), compared with 34.6% for a treatment duration of greater than 4 months (6 studies, 107 patients).

Timing.

Patients who received somatostatin as first-line therapy were significantly more likely to report a positive tumour response than those who had received other therapies first, 69.5 versus 28.5% (p<0.006). Toxicity and drop-outs.

Specific side-effects were reported in 25.4% of the patients in 11 studies involving 185 patients. The most common side-effects were nausea and vomiting (6%), abdominal pain or cramping (9%), and diarrhoea (11%). All of the side-effects were resolved once the treatment was stopped. The use of somatostatin analogues was discontinued in 3 patients because of severe side-effects.

Authors’ conclusions
In patients with metastatic breast cancer, treatment with somatostatin was associated with a tumour response of over 40%, with few side-effects. The best results were achieved when somatostatin analogues were given as a first-line therapy.

CRD commentary
The aims were stated, and the inclusion criteria were defined in terms of the participants, intervention and outcomes. Several relevant sources were searched for published and unpublished studies and no language restrictions were applied, although the full details of the databases searched were not reported. However, the methods used to select the studies were not described, and the inclusion criteria were not defined in terms of the study design.

Validity was not assessed, and the limitations of evidence provided by uncontrolled trials with small sample sizes were not commented upon. Some relevant data were extracted, but the study design and the methods used to extract the data were not described. The data were combined in a meta-analysis without a prior assessment or discussion of the statistical heterogeneity. The influence of various factors on the results was explored. The findings of this review must be viewed as exploratory rather than definitive given the following limitations: the methods used to conduct this review were not reported; the validity and statistical heterogeneity of the studies were not assessed; and the conclusions were based on uncontrolled studies with small sample sizes.

Implications of the review for practice and research
Practice: The authors state that somatostatin analogues (either octreotide or lanreotide), at a dose of 2 mg/day for 4 months, may be considered as an initial treatment for women with breast cancer who develop metastatic disease.

Research: The authors state that further studies are required to determine which patients are more likely to respond to therapy, and to determine the role of combination therapy (somatostatin analogue plus tamoxifen plus an anti-prolactin).

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