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SHORT REPORTS

Cyclical sequential hormonochemotherapy in advanced breast cancer

Endocrine treatment or chemotherapy is widely used for patients with breast cancer, and the response rate remains more or less constant at about 30-40%. Using hormonal treatment to render the cancer cells more susceptible to cytotoxic chemotherapy was proposed by Lippman[1] and Allegra *et al*.[2] We report using oestrogen at a physiological concentration to bring stem cells out of the resting phase and to stimulate cell division into partial synchrony. High dose progestogen is then given, which, by reducing the receptor state of the cancer cells, is designed to enhance their susceptibility to the subsequent cytotoxic chemotherapy. This was administered cyclically and sequentially at three week intervals in accordance with the stem cell kinetic data of Skipper[3] and Hill.[4]

Patients, methods, and results

Forty women presenting with advanced breast cancer were treated with our regimen. All were postmenopausal (mean age 63 (SD 11) years), with the exception of two patients aged 30 and 36. The diagnosis of advanced breast cancer was based on finding one or more of the following: metastases in bone (eight cases), lung (six), or liver (seven) or fixity of axillary lymph nodes (17) and large tumour size (mean 7·5 (SD 3·9) cm).

Patients received three double cycles of hormonochemotherapy. Hormonal treatment was initiated with ethinyloestradiol for one week (10 μg/day) followed by medroxyprogesterone acetate for two weeks (500 mg/day intramuscularly). At the end of the first three week period of hormonal treatment the patient received a bolus injection of vincristine (2 mg intravenously) and an infusion of doxorubicin (50 mg intravenously). The hormonal treatment was then repeated for a further three weeks—that is, one week of oestrogen, two weeks of progestogen—at the end of which an infusion of cyclophosphamide (500 mg), methotrexate (50 mg), and 5-fluorouracil (500 mg) was given. This constituted one double cycle, and patients received three of these cycles. Response to treatment was assessed according to criteria of the International Union Against Cancer.[5]

Thirty four of the 40 patients completed three double cycles of treatment. Of these, 16 showed a complete response, 15 a partial response, and only three no response, giving an overall response rate of 91%. The six patients who did not complete the treatment died of their disease before they had finished one cycle. The mean disease free interval for patients showing a complete response was 22·0 months and was significantly longer ($p<0·05$) than the 11·6 months for partial responders.

The table shows the response by metastatic site together with the average duration of disease free interval for patients achieving a complete or partial response. The overall response at these sites approached 90%.

Response in metastatic sites

Site	No	No (%) showing complete response	Mean duration (months)	No (%) showing partial response	Mean duration (months)	Overall response (%)
Advanced local disease or lymph node fixity, or both	17	7 (41)	22	8 (47)	6	89
Bone	8	2 (25)	23	6 (75)	5	100
Lung	6	2 (33)	21	3 (50)	7	83
Liver	7	1 (14)	24	5 (71)	6	85

Comment

The results of this study in which women with advanced metastatic breast cancer were treated with three double cycles of sequential hormonochemotherapy are very encouraging. Over 90% of the women showed some degree of objective response. Furthermore, the 16 (47%) patients who obtained a complete response by established criteria[5] had a disease free interval of 22 months. The response to hormonal treatment alone in unselected patients is usually about 30%, which may improve to about 60% in patients selected on the basis of their oestrogen receptor state. The response to chemotherapy may be higher but is usually between 30% and 60%. The disease free interval in patients treated with either hormonal treatment or chemotherapy is usually less than one year.

As hormones and drugs are thought to act by different mechanisms and against different cell populations, we have combined hormonal treatment with chemotherapy. We have not, however, simply used these two forms of treatment in an adjuvant synchronous manner but have attempted to use the hormones in such a way as to bring the stem cells out of their resting phase and make them more susceptible to cytotoxic drugs: hence cyclical sequential hormonochemotherapy.

Our results suggest that using hormonal and cytotoxic treatment in a cyclical sequential combination may significantly improve the response rate compared with using either treatment alone and provides a useful prolongation of life.

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The Breast Clinic, St Mary's Hospital, London W2 1NY
MARGARET W GHILCHIK, MS, FRCS, consultant surgeon
N A SHAIKH, FRCS, surgical registrar

Department of Chemical Pathology, St Mary's Hospital Medical School, London W2 1PG
P A BERANEK, MB, PHD, lecturer
M J REED, MSC, PHD, senior lecturer

Correspondence to: Mrs Ghilchik.