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Oestrogen Receptor in Human Breast Cancer Tissue and Response to Endocrine Therapy

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Summary

Oestrogen receptor determinations were done in metastatic breast cancer tissue of patients with advanced breast cancer. In 37 patients with progressive disease evaluation of the response to endocrine treatment was possible, following the criteria of the E.O.R.T.C. Co-operative Breast Cancer Group. In 20 patients with receptor-negative tumours two objective remissions were noted; in 17 patients with receptor-positive tumours 14 objective remissions were seen. There seems to be a striking correlation between the presence or absence of oestrogen receptor in tumour tissue and the clinical response to hormonal therapy.

Introduction

A correlation between the presence of a specific oestrogen receptor in breast cancer tissue and the response to endocrine treatment has been shown in rats (King *et al.*, 1965; King *et al.*, 1966; Jensen *et al.*, 1967; Trams and Maass, 1969). Evidence for a similar correlation in human breast cancer was reported by Jensen *et al.* (1972) and Maass *et al.* (1972). An increased in-vivo uptake of injected radiolabelled oestrogens by human breast cancers was also shown in patients who subsequently responded to endocrine therapy (Folca *et al.*, 1961; Braunsberg *et al.*, 1973).

In our institute oestrogen receptor determinations have been carried out since 1971 in primary breast cancers and in biopsy specimens taken from skin and lymph node metastases. In 37 patients with progressive advanced breast cancer the clinical response to endocrine treatment has now been evaluated and compared with the results of receptor determinations in metastases sampled for biopsy shortly before the start of therapy. In 20 of these patients the treatment and follow-up were part of a clinical trial of the E.O.R.T.C. Breast Cancer Group.

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Patients and Methods

The oestrogen receptor determinations were done in tissue homogenates by a charcoal separation technique (Korsten and Persijn 1972). All tissue specimens were taken from skin and lymph node metastases. In all tissue samples the presence of tumour was verified histologically. Therapy was started after the specimen had been taken but before the receptor content was known. All the patients had evidence of progressive disease and had lesions which could be evaluated objectively (skin and lymph node metastases, lung metastases, well-defined osteolytic bone metastases). The patients were investigated and followed up according to the criteria outlined in the E.O.R.T.C. Co-operative Breast Cancer Group protocol (G.E.C.A., 1967).

An objective remission was accepted when measurable regression was noted in at least half of the lesions, without progression in any lesion and without any new lesion arising anywhere. The improvement had to last for more than three months. In four patients who responded well to treatment and who had no evidence of bone metastases no follow-up skeletal *x*-ray films were obtained.

Endocrine therapy was thought to be indicated only when the disease was too widespread to be controlled by palliative radiotherapy or when progression was noted in irradiated areas. Nine premenopausal women underwent oophorectomy; the other 28 patients were two or more years postmenopausal and were treated with either ethinyloestradiol (Lynoral) 3 mg daily or nandrolone phenylpropionate (Durabolin) 25 mg three times a week or nafoxidine (U 11100) 180 mg daily. Nafoxidine is an oestrogen antagonist which was shown to produce remission in about 30% of cases of advanced breast cancer in type 1 and type 2 clinical trials carried out by the E.O.R.T.C. Breast Cancer Group (1972, 1973). In 35 patients this was the first endocrine treatment given. Two patients had had endocrine therapy (oophorectomy, ethinyloestradiol) previously but the biopsy specimens were taken when there was a recurrence of the progressive disease and the preceding therapy had been stopped for more than six weeks.

Results

Out of 17 patients found to have receptor in their tumour tissue 14 experienced an objective remission (table I). Of the 20 patients in whom the tumour tissue was receptor-negative only two had an objective remission (table II). Application of the X^2 test gave $P < 0{\cdot}00001$. There seemed to be no relation between the quantity of receptor measured and the quality and duration of the remission obtained. The amounts of receptor

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TABLE I—*Response of Receptor-positive Cases*

Therapy	No. of Patients	Objective Remission
Ethinyloestradiol	5	4
Nafoxidine	7	5
Nandrolone phenylpropionate	3	3
Oophorectomy	2	2
Total	17	14

TABLE II—*Response of Receptor-negative Cases*

Therapy	No. of Patients	Objective Remission
Ethinyloestradiol	5	1
Nafoxidine	8	
Oophorectomy	7	1
Total	20	2

varied between 7,600 and 630,000 c.p.m./g of tissue (negative, less than 4,000; positive, more than about 8,000) (Korsten and Persijn, 1972). Most positive tissues contained between 20,000 and 40,000 c.p.m./g of tissue.

Of the three receptor-positive patients who did not have objective remissions two experienced subjective remission—that is, noticeable subjective improvement without further progression but without measurable tumour regression. One of these two patients continued with excellent subjective remission after 13 months on ethinyloestradiol treatment; the other patient died of coronary thrombosis after two and a half months, though still in subjective remission with nafoxidine. The third patient did not experience any benefit from nafoxidine or from ethinyloestradiol given later.

One receptor-positive patient had a remission during nafoxidine treatment and when the remission was over nafoxidine was stopped. Some weeks later receptor could not be found in a biopsy specimen, and the introduction of ethinyloestradiol treatment had no effect.

Two receptor-positive patients who had previously experienced remissions (oophorectomy, ethinyloestradiol) showed an objective remission with nandrolone and nafoxidine respectively.

In three receptor-negative patients two treatments were studied sequentially—one patient did not react to nafoxidine or to ethinyloestradiol and one did not react to ethinyloestradiol or to nafoxidine (in that order); the third patient, however, who had not responded to ethinyloestradiol, later obtained an objective remission with nandrolone.

Two patients developed a hypercalcaemia within a few days after the start of treatment (ethinyloestradiol and nafoxidine respectively). The tumours of these patients contained exceptionally high levels of receptor—500,000 and 630,000 c.p.m./g of tissue. In one patient therapy (nafoxidine) was resumed after a few days in which the hypercalcemia had subsided; she obtained a remission, which continued 11 months later. The other patient, who is not included in this study, had a severe hypercalcaemia which required high doses of corticosteroids. She was further treated with prednisone and low doses of cyclophosphamide, and under this treatment she had an objective remission. Since cyclophosphamide was used the remission cannot be regarded as a response to endocrine treatment.

Discussion

Our results seem to confirm the observations of others (Jensen *et al.*, 1972; Maass *et al.*, 1972), that the presence of oestrogen receptor in human breast cancer can be correlated with the hormone responsiveness of the tumour. When comparing results it may be important to take into account the fact that all receptor determinations in this study were done in advanced cases and in metastases which were accessible for biopsy—namely in skin, and lymph node metastases. As Jensen *et al.* (1972) pointed out, receptor levels may vary in metastases taken from different locations in the same patient so that the result from one biopsy need not always be representative for all tumour tissue present in the same patient. In our patients we have no data on the receptor content of the primary tumour or of lung, bone, or liver metastases.

In one patient treated with ethinyloestradiol we observed almost complete regression of a large inoperable primary tumour and of all lymph node metastases, while at the same time there was rapid progression of skeletal metastases. The receptor assay in a lymph node specimen in this case gave a negative result.

In our group of patients the correlation was not absolute. Two receptor-negative patients obtained remissions under endocrine therapy; in one of them, who reacted favourably to an oophorectomy, the possibility that a modest amount of receptor could not be detected because it was saturated by naturally occurring oestrogens cannot be ruled out. Maass *et al.* (1972) provided evidence that receptor cannot be shown in tissues from patients with high levels of plasma oestradiol. In the other receptor-negative case there were no clinical features to suggest an explanation for the discrepancy. One patient with a receptor-positive tumour did not experience any beneficial effect at all (ethinyloestradiol, nafoxidine). The two receptor-positive patients who had subjective remissions are mentioned above.

In several patients the effects of more than one endocrine therapy could be studied. One receptor-positive patient had a remission with nafoxidine but did not respond to ethinyloestradiol; the three receptor-positive patients who responded to their first and second treatments have already been described.

Three receptor-negative patients had two sequential treatments; two of them showed no response to nafoxidine or ethinyloestradiol but the third patient who had not responded to ethinyloestradiol obtained an objective remission later with nandrolone.

The development of hypercalcaemia in two patients with exceptionally high receptor levels supports the opinion that the hypercalcaemia after additive hormonal treatment might be an expression of extreme hormone sensitivity of the tumour rather than of progression of the disease. It is attractive to speculate that this excessive specific oestrogen binding capacity of the tumour could be responsible for disturbing the endocrine mechanisms regulating calcium metabolism.

Evidence is accumulating rapidly that the chance of obtaining a remission in advanced breast cancer is very small when the tumour does not contain specific oestrogen receptor. Our results suggest that though a good correlation can be shown a single receptor determination can be used for only a rough prediction of the hormone responsiveness of the tumour. On the other hand, the question whether it is still justifiable to submit patients to major ablative surgery without regard to the presence of oestrogen receptor in the tumour is already a very urgent one.

We wish to thank the surgeons and pathologists at the institute for their co-operation in obtaining the biopsy material needed for these investigations. We also thank the staff of the department of internal medicine at the Institut Jules Bordet in Brussels for their efforts in reviewing the trial cases to decide on the effect of the treatment.

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Requests for reprints should be addressed to Dr. E. Engelsman.

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PRELIMINARY COMMUNICATIONS

Hypergastrinaemia in Rheumatoid Arthritis: Disease or Iatrogenesis

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Introduction

The interplay of rheumatoid arthritis, peptic ulceration, and anti-inflammatory drug therapy remains highly complex and poorly understood. Recent advances in the technology of the measurement of intestinal hormones provide a new approach to the problem. We report an unexpectedly high incidence of markedly raised plasma gastrin levels in rheumatoid arthritis.

Materials and Methods

Fifty patients with classical or definite rheumatoid arthritis (Ropes *et al.*, 1959) were studied. The mean age (± S.E. of mean) was 54 ± 1·58 years. A group of 100 control subjects, mean age 55 ± 2 years without known rheumatoid arthritis, pernicious anaemia, or gastrointestinal disease, were also studied. The clinical features of the patients with rheumatoid arthritis are summarized in the table. These patients comprised consecutive admissions to the Centre for Rheumatic Diseases over a period of one month.

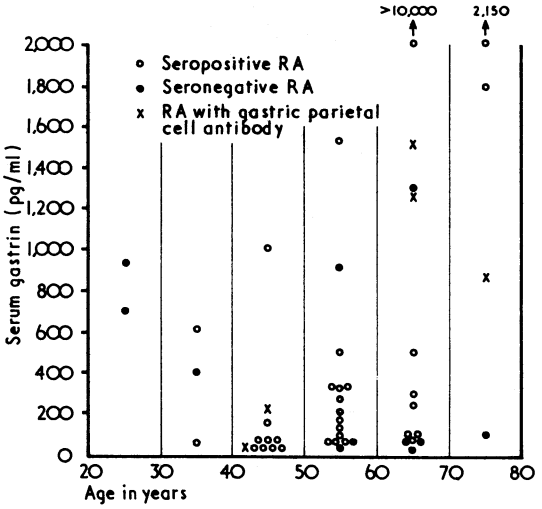
The following clinical and laboratory data were recorded in all patients with rheumatoid arthritis in addition to age and sex: clinical articular index of joint tenderness (Ritchie *et al.*, 1968), presence or absence of subcutaneous nodules; haemoglobin concentration; white cell count; erythrocyte sedimentation rate (E.S.R.); plasma proteins; titre of rheumatoid and antinuclear factors; gastric parietal cell autoantibody; and joint *x*-ray appearances. A record of past and present drug therapy was made and each patient was carefully questioned regarding dyspepsia. Those with a history of dyspepsia had a barium-meal examination.

The plasma gastrin was measured using a sensitive and specific radioimmunoassay. The assay uses antibody raised in rabbits to synthetic human gastrin.

Labelled hormone is prepared using a modification of the chloramine-T method of Hunter and Greenwood (1962) and separation of free hormone from that bound to antibody is achieved by treatment of the assay incubate with dextran-coated charcoal (Buchanan and McCarroll, 1971). Precision is greatest below 600 pg/ml and the sensitivity of the assay—that is, the lowest concentration of gastrin which can be differentiated from zero—is 10 pg/ml. Cross-reaction with cholecystokinin and pancreozymin is minimal, and preliminary studies show that the antibody recognizes not only the heptadecapeptide but also the "big gastrin" described by Yalow and Berson (1971).

Results

The clinical features and laboratory indices in the rheumatoid arthritis patients are summarized in the table, and the fasting plasma gastrin levels in these patients are shown in the chart. The mean (± S.E. of mean) fasting plasma gastrin level of



Fasting plasma gastrin levels in patients with rheumatoid arthritis.

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