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Contribution of Prednisolone to the Primary Endocrine Treatment of Advanced Breast Cancer

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Abstract—*Two hundred and four patients with progressive locally advanced or metastatic breast cancer not controllable by local therapy alone, and who had had no prior systemic therapy for advanced disease, were treated by primary endocrine therapy according to menopausal status. Premenopausal patients received ovarian irradiation (O) whilst postmenopausal patients received tamoxifen 10 mg b.d. (T). Patients were randomised to receive either no additional treatment or prednisolone 5 mg b.d. (P). In 180 evaluable patients, T+P induced significantly more responses than T alone (26/73 vs 9/72, P <0.01) and the addition of P to O in premenopausal patients also induced more responses than O alone (7/16 vs 4/19), but this difference was not significant and accrual of premenopausal patients continues. There was a trend for patients receiving T+P to have a longer survival than those receiving T alone (median 25 vs 16 months). These trends occurred in patients with tumours positive for oestrogen receptors and when receptor status was unknown; patients with receptor-negative tumours had a negligible response to endocrine treatment. P mitigated the occurrence of hypercalcaemia and tumour flare sometimes seen with T alone.*

INTRODUCTION

ENDOCRINE therapy is the usual initial systemic treatment for disseminated breast cancer; ovarian ablation being preferred in premenopausal patients and additive hormonal therapy in postmenopausal patients. Ovarian ablation by surgical oophorectomy has a response frequency of approximately 30% [1] and ovarian radiation gives similar results [2]. In postmenopausal patients tamoxifen has largely replaced oestrogens and androgens as the initial treatment of choice because of the much lower incidence of side-effects, although the response rate is similar [3]. The frequency of response to tamoxifen in postmenopausal patients is about 32% [4] and its mode of action is thought to be by competitive binding to oestrogen receptors in the target tissue [5].

Prednisolone is also an active agent in disseminated breast cancer, inducing remissions in 14% of patients over 65 years of age and disease stabilisation for at least 6 months in a further 21% [6]. The mechanism of action of prednisolone in advanced breast cancer, although not entirely clear, probably depends substantially on decreased production of adrenal sex hormones following prednisolone-induced adrenal atrophy [7], although it may be partially mediated by corticosteroid receptors which are found in breast tumour cells [8]. Furthermore, in premenopausal women aged 45 or over the addition of prednisolone to ovarian irradiation as adjuvant therapy after mastectomy leads to a statistically significant reduction in recurrence rates and improved survival, a benefit not found with ovarian irradiation alone [9].

Hence it was of interest to undertake a trial to test the combination of ovarian irradiation + prednisolone against ovarian irradiation alone in premenopausal patients and to compare a combination of tamoxifen and prednisolone against

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tamoxifen alone in postmenopausal patients with advanced breast cancer. The preliminary results of this trial are reported here.

MATERIALS AND METHODS

Patients

Patients were eligible for entry into this trial if they had evaluable progressive locally advanced or metastatic breast cancer, confirmed histologically and not controllable by local therapy alone, and had not been given previous endocrine or other systemic therapy for advanced disease. Patients who had received adjuvant chemotherapy after mastectomy or combined with radiotherapy for primary locally advanced disease were regarded as eligible, but not patients who had received adjuvant endocrine therapy.

Patients were ineligible if: (a) they had received systemic corticosteroid therapy in the previous year; (b) there was a history of a previous malignancy elsewhere; (c) there were medical contraindications to the use of corticosteroids; (d) immediate chemotherapy was thought advisable because of rapidly progressive life-threatening disease; and (e) there was hypercalcaemia, not controllable without the use of steroids.

Treatment at first diagnosis had been in the context of several clinical trials. For patients with operable breast cancer, treatments included modified radical mastectomy only, modified radical mastectomy with adjuvant chemotherapy (either melphalan or a combination of cyclophosphamide, methotrexate and 5-fluorouracil) or adjuvant radiotherapy, wide excision or simple mastectomy with radiotherapy. Patients with locally advanced disease at presentation were treated by either radiotherapy alone or combined with cytotoxic chemotherapy.

Menopausal status

Before randomisation for treatment, patients were stratified according to menopausal status in order to determine the appropriate endocrine therapy.

(a) Patients who had had a menstrual period within the previous 6 months were regarded as premenopausal, while if the last menstrual period was 6 months ago or longer, patients were deemed postmenopausal.

(b) Patients with a previous hysterectomy and retention of one or both ovaries were regarded as premenopausal if < 50 years of age and postmenopausal if $\geqslant 50$ years of age.

(c) Premenopausal patients who ceased menstruating whilst on adjuvant chemotherapy and then relapsed whilst receiving, or within 6 months of stopping, chemotherapy were considered premenopausal. If relapse occurred 6 months or more after stopping adjuvant chemotherapy the menopausal status was as in (a) above.

Treatment

Premenopausal patients were randomised to receive either: (a) ovarian irradiation alone 1200 cGy central dose to pelvis in 4 days by opposed fields with external beam megavoltage therapy (O); or (b) O plus prednisolone 5 mg b.d. (P) commencing on the first day of radiotherapy (O+P).

Postmenopausal patients were randomised to receive either: (a) tamoxifen 10 mg b.d. (T); or (b) tamoxifen plus prednisolone 5 mg b.d. (T+P).

Treatment was continued until there was evidence of progressive disease.

Study parameters

Before entry into the trial, a full physical examination was performed, measurements were made of all palpable lesions and all visible lesions were photographed. All patients had a chest radiograph, bone scintiscan with radiographs of areas of increased isotope uptake, liver scintiscan, full blood count and biochemical screen. Baseline lesions were selected for serial assessment. Patients were followed up at 4-weekly intervals with repeat assessment of baseline lesions and photographs. Both scintiscans, chest radiographs of skeletal lesions, full blood counts and biochemical screens were repeated every 3 months.

Response criteria

Objective response was assessed by UICC criteria [10]. Briefly, the following categories of response were recognised.

(a) Complete response—disappearance of all known disease. In the case of lytic bone metastases, these must have been shown radiologically to have calcified.

(b) Partial response—a $\geqslant 50\%$ decrease in the sum of the products of the perpendicular axes of measurable lesions and objective improvement in evaluable, but non-measurable, lesions; no new lesions. It was not necessary for every lesion to have regressed but no lesion should have progressed.

(c) No change—lesions unchanged (ie less than 50% decrease or less than 25% increase in the size of measurable lesions).

(d) Progressive disease: mixed—some lesions regress while others progress or new lesions appear; failure—progression of some or all lesions and/or appearance of new lesions. No lesion regresses.

Duration of response

In patients with an objective regression, its duration was dated from the start of therapy until either new lesions appeared or any one existing lesion increased by 25% or more above the smallest size recorded.

Survival

Survival was estimated from the date of commencement of treatment to death.

Extramural review

The records of all responders up to December 1980 were reviewed by two external independent observers; the records of all non-responders and all responders since December 1980 have been internally reviewed.

Statistical methods

Survival and duration of response were analysed by the log rank method [11]. The significance of differences between binary variable was calculated by the chi square test for one degree of freedom.

Oestrogen receptors (ER)

In the majority of patients ER content of primary or metastatic tumour was estimated by the method of King *et al.* [12]. A value of $\geqslant 5$ fmol receptor/mg cytosol protein was regarded as positive (ER+) and any value <5 fmol receptor/mg cytosol protein as negative (ER−).

RESULTS

From August 1978 to October 1981, 204 patients were entered in this study. Fourteen patients have been excluded from this analysis because at review major protocol infringements had occurred. These consisted of 3 patients with medical contraindications to use of steroids, 1 patient who was already taking steroids, 1 patient who failed to take medication, 2 patients who were lost to follow-up before response could be assessed, 3 patients found at review to have had no evidence of recurrent disease at the time of randomisation, 1 patient who received inappropriate treatment for her menstrual status, 3 patients with a previous non-breast malignancy and 1 patient who received concurrent chemotherapy. The records of a further 10 patients were found to be inadequate for assessment of response, but these patients are included in analysis of survival.

Table 1 shows the characteristics of the 180 evaluable patients. Although patients were randomly allocated to each treatment group, there was a trend for more patients who received standard treatment + prednisolone to have ER+ tumours compared to those given standard therapy alone. This difference occurred only in postmenopausal patients; 47/73 (64%) of these who were allocated to receive T+P had ER+ tumours compared to 35/72 (49%) allocated to receive T only. This difference in distribution of ER+ tumours and the slight preponderance of stage I and II tumours in the group allocated to receive T+P is compatible with the longer median disease-free interval and median time from diagnosis to trial entry observed in this group of patients. This disparity is taken into account in the analysis below. Treatments received at presentation were comparable for each group (Table 2). The sites of disease at commencement of endocrine therapy for each treatment subgroup are shown in Table 3, there being no significant differences.

Response categories are shown in Table 4. Patients allocated to receive standard endocrine therapy + prednisolone had a significantly higher response rate compared to patients allocated to receive standard therapy only ($P<0.001$). Although the addition of prednisolone to ovarian ablation was observed to produce more responses

Table 1. *Patient characteristics*

	Treatment category			
	Premenopausal		Postmenopausal	
	O	O+P	T	T+P
Total number of assessable patients	19	16	72	73
Mean age at entry (years)	42	42	62	59
Stage at presentation I and II	14	14	42	48
(number of patients): III and IV	5	2	30	25
Median disease-free interval (months)	17	11.5	19	22
Range disease-free intervals (months)	0–60	0–46	0–180	0–228
Median time from diagnosis to entry (months)	23	21	27	31
Range times from diagnosis to entry (months)	4–62	0–47	0–276	0–245
Oestrogen receptor (ER) status:				
ER $\geqslant$ 5 fmol/mg cytosol protein	9	7	35	47
ER $<$ 5fmol/mg cytosol protein	3	4	14	7
ER not known	7	5	23	19

Table 2. Previous treatment at presentation

Initial therapy	Treatment category: Irradiation menopause (n = 19)	Irradiation menopause + prednisolone (n = 16)	Tamoxifen (n = 72)	Tamoxifen + prednisolone (n = 73)
Radical mastectomy only	7	6	20	21
+ adjuvant chemotherapy	2	3	7	11
+ radiotherapy	2	2	5	10
Wide excision or simple mastectomy + radiotherapy	3	3	11	7
Radiotherapy only	5	1	11	9
Radiotherapy + chemotherapy	0	0	7	3
No previous treatment	0	1	11	12

Table 3. Sites of disease at commencement of endocrine therapy

	Irradiation menopause (n = 19)	Irradiation menopause + prednisolone (n = 16)	Tamoxifen (n = 72)	Tamoxifen + prednisolone (n = 73)
Soft tissue	16 (16)	10 (10)	45 (45)	51 (51)
Bone	11 (7)	12 (7)	42 (32)	42 (35)
Lung	7 (5)	1 (1)	21 (21)	16 (15)
Pleura	2 (1)	3 (1)	5 (5)	13 (6)
Liver	1 (1)	1 (1)	10 (8)	8 (7)
Other	*1 (0)	0	*1 (1)	0

*Abdominal mass.
Figures in parentheses refer to number of sites of disease that were assessable by UICC criteria.

Table 4. Overall response categories

Response categories	Irradiation menopause	Irradiation menopause + prednisolone	Tamoxifen	Tamoxifen + prednisolone
Complete remission	1	1	0	3
Partial remission	3 } 4 (21%)	6 } 7 (44%)	9 } 9 (13%)	23 } 26 (36%)
No change	1	2	7	9
Progressive disease mixed	2	2	6	4
Progressive disease failure	12	5	50	34
Total	19	16	72	73

Table 5. Objective regressions for each site of assessable disease

	Irradiation menopause	Irradiation menopause + prednisolone	Tamoxifen	Tamoxifen + prednisolone
Soft tissue	6/16 (38%)	5/10 (50%)	5/45 (11%)	28/51(55%) $P<0.001$
Bone	2/7	2/7	2/32 (6%)	4/35(11%)
Lung	1/5	1/1	5/21 (24%)	5/15(33%)
Pleura	0/1	0/1	1/5	0/6
Liver	0/1	0/1	0/8	0/7
Other	—	—	0/1	—

Numerator: number of regressions; denominator: number of sites of assessable disease.

Table 6. Objective regression and tumour oestrogen receptor (ER) content

ER in fmol/mg cytosol protein	Irradiation menopause	Irradiation menopause + prednisolone	Tamoxifen	Tamoxifen + prednisolone
< 5	0/3	1/4	0/14	0/7
5–10	0/3	0/0	0/3	1/2
11–50	3/4	2/3	2/13	6/20
51–100	0/2	1/2	1/8	7/13
> 100	0/0	1/2	3/11	5/12
All ER + (≥5)	3/9	4/7	6/35	19/47
ER not known	1/7	2/5	2/23	7/19

than ovarian ablation alone, this was not statistically significant in this small group of patients. T+P induced significantly more responses than T alone ($P<0.01$).

Table 5 shows the objective regression frequency for each site of assessable disease. The addition of prednisolone to tamoxifen produced significantly more remissions at the most common site of assessable disease (soft tissue). All treatments were equally ineffective at inducing objective regression of metastatic hepatic disease.

In Table 6, objective regressions for each treatment are shown according to tumour ER content. There was a trend for more responses in patients receiving T+P for each ER subgroup. The addition of prednisolone to standard therapy induced more responses in both ER+ and ER- unknown tumours, and for ER+ tumours this difference was significant, with 9/44 (20%) responses to standard therapy whilst the addition of prednisolone produced 23/54 (43%) responses ($P<0.025$). When postmenopausal patients with ER+ tumours were assessed, only 6/35 (17%) responded to T compared to 19/47 (40%) who responded to T+P ($P<0.025$). There was only 1 response in 25 patients with ER- tumours.

Response duration and survival

Median response duration was 13 months in both patients receiving standard therapy and standard therapy + prednisolone. Response duration was similar in patients whose tumours were ER+ or of unknown receptor status.

Median survival for all patients from entry on this study was 16.5 months. Survival of responders to endocrine treatment was significantly longer than non-responders (median 26 vs 13 months, $P<0.001$). Similarly, patients with stable disease (response + no change) had a prolonged median survival compared to patients with progressive disease (median 26 vs 10.5 months, $P<0.001$). There was no difference in survival between patients receiving O (19 months) and patients receiving O+P (18 months). Postmenopausal patients receiving T+P had a significantly longer survival than those receiving T alone (median 21 vs 12 months, $P<0.025$) (Fig. 1). Survival from entry also depended on ER status (Fig. 2). To

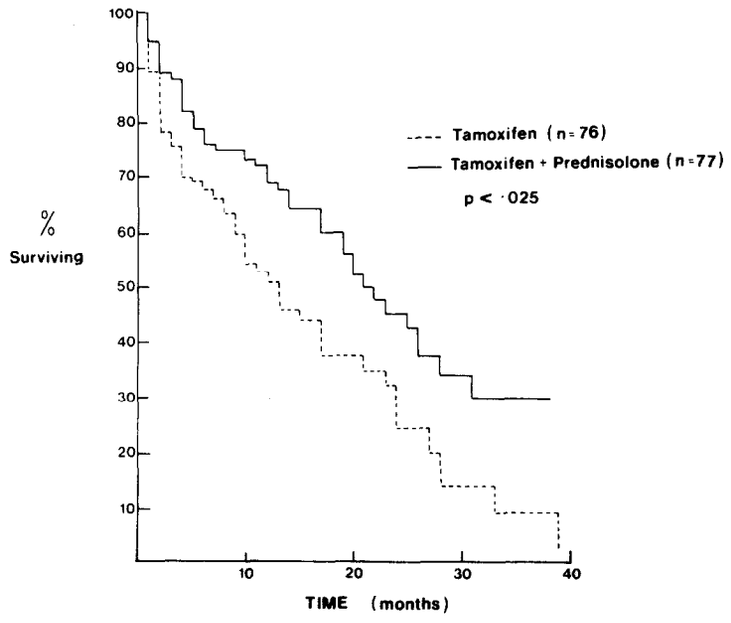

Fig. 1. Survival from first endocrine treatment in postmenopausal patients.

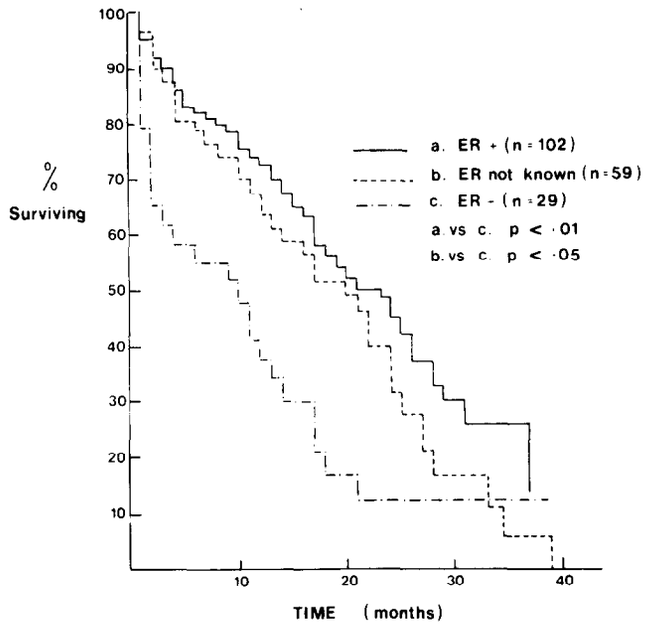

Fig. 2. Survival from first endocrine treatment and tumour ER status.

allow for the disparity in distribution of receptor-rich and receptor-poor tumours in postmenopausal patients, survival from study entry was analysed according to treatment received and tumour receptor content. In postmenopausal patients whose tumours were ER+ there was a trend for prolonged survival in patients treated with T+P compared with those treated with T alone (median 25 vs 16 months), but this was not significant. The subsequent treatments received by patients on the development of progressive disease are summarised in Table 7.

Side-effects

Treatment was in general well tolerated in most patients and side-effects are outlined in Table 8.

Table 7. Subsequent systemic therapy after failure of initial endocrine therapy

	Number of patients			
	Premenopausal		Postmenopausal	
Subsequent systemic therapy	O	O+P	T	T+P
Chemotherapy	12	6	20	19
Oestrogens	—	—	1	2
Steroids	—	—	1	—
Progestogens	—	—	3	2
Androgens	—	—	—	1
Tamoxifen	5	3	—	—
Aminoglutethimide	—	1	1	2
Hypophysectomy	1	1	—	—

Table 8. Side-effects

	Irradiation menopause (n = 19)	Irradiation menopause + prednisolone (n = 16)	Tamoxifen (n = 72)	Tamoxifen + prednisolone (n = 73)
Tumour flare	0	0	4*	0
Gastro intestinal (nausea, diarrhoea, dyspepsia)	0	0	2	5
Hypercalcaemia	0	0	5*	0
Weight Gain	0	1	0	5
Other	0	1†	0	0

*Responses in these patients were: tumour flare, 2PDF, 1PDM, 1NC (all ER not known); hypercalcaemia, all PDF (2EF+, 2ER–, 1ER not known).

†Acne.

Two patients on the tamoxifen only arm of the study needed systemic steroids to lower serum calcium. Because of a suggestion that tamoxifen-induced hypercalcaemia [13] or exacerbation of bone pain (flare) may be associated with a subsequent response to tamoxifen, the eight patients experiencing these effects were studied separately and all failed to respond. There was no relationship between side-effects and tumour ER status. These side-effects did not occur in patients treated with concomitant prednisolone. No patient had treatment interrupted because of side-effects.

DISCUSSION

Previous reports have indicated that the combination of tamoxifen with other hormonal treatment therapies [14, 15] (diethylstilboestrol, medroxyprogesterone acetate) has no advantage over the use of tamoxifen alone. By contrast, in this trial the addition of prednisolone to tamoxifen led to a significantly higher response frequency in postmenopausal women with advanced breast cancer than in those receiving tamoxifen alone. However, the response to tamoxifen of 17% in patients with ER+ tumours in this study was unexpectedly low, but could not be accounted for by any disparity in other prognostic variables. Furthermore, the response frequency to T+P of 36% may be similar to that expected from tamoxifen alone [4]. Hence it is possible that these results have arisen by chance.

Although preliminary results suggest that the addition of prednisolone to ovarian ablation confers a similar advantage in premenopausal patients over ovarian ablation alone, too few patients have so far been studied for any differences to be statistically significant.

Combined tamoxifen and prednisolone was also associated with a lengthened survival compared to tamoxifen alone. It is not known whether using prednisolone sequentially after tamoxifen alone would have achieved similar results and this is now being tested in another trial which will also assess whether the results of the present study can be confirmed.

An additional advantage of prescribing prednisolone with tamoxifen is the apparent elimination of hypercalcaemia and tumour flare sometimes seen when the antioestrogen is used alone, although tamoxifen is usually well tolerated.

The negligible response rate in patients with ER- tumours reinforces the view that trials of endocrine therapy should be restricted to patients with tumours which are ER+ or of unknown receptor status.

Our tentative conclusion from this trial is that the addition of prednisolone to tamoxifen in postmenopausal patients may lead to a significantly higher response frequency, but that because of the observed unexpectedly low response frequency to tamoxifen alone, further studies are needed to confirm these findings.

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REFERENCES

1. VERONESI U, PIZZOCARCO G, ROSSI A. Oophorectomy for advanced carcinoma of the breast. *Surg Gynecol Obstet* 1975, **141**, 569–570.
2. LEES A, GIUFFRE C, BURNS P, HARLBART M, JENKINS H. Oophorectomy versus radiation ablation of ovarian function in patients with metastatic carcinoma of the breast. *Surg Gynecol Obstet* 1980, **151**, 121–124.
3. INGLE J, AHMANN D, GREEN S *et al.* Randomised clinical trial of diethylstilboestrol versus tamoxifen in postmenopausal women with advanced breast cancer. *N Engl J Med* 1981, **304**, 16–21.
4. MOURIDSEN H, PALSHOF T, PATTERSON J, BATTERSBY L. Tamoxifen in advanced breast cancer. *Cancer Treat Rev* 1978, **5**, 131–141.
5. LIPPMAN M, BOLAN G, HUFF K. The effects of estrogens and antioestrogens on hormone-responsive human breast cancer in long term tissue culture. *Cancer Res* 1976, **36**, 4595–4601.
6. MINTON MJ, KNIGHT RK, RUBENS RD, HAYWARD JL. Corticosteroids for elderly patients with breast cancer. *Cancer* 1981, **48**, 883–887.
7. JANTET G, CROCKER D, SHIRAKI M, MOORE F. Adrenal suppression in disseminated carcinoma of the breast I. The effect on adrenal morphology of hypophysectomy and corticosteroid treatment. *N Engl J Med* 1963, **269**, 1–7.
8. WITTLIFF J, SAVLOV E. Biochemical basis for the selection of hormonal manipulation in the patient with breast carcinoma. *Int J Radiat Oncol Biol Phys* 1978, **4**, 463–467.
9. MEAKIN JW, ALLT WEG, BEALE FA *et al.* Ovarian irradiation and prednisolone following surgery for carcinoma of the breast. In: SALMON SE, JONES SE, eds. *Adjuvant Therapy of Cancer.* Amsterdam, Elsevier, 1977, **4**, 463–467.

10. HAYWARD JL, CARBONE PP, HEUSON J-C, KUMAOKA S, SEGALOFF A, RUBENS RD. Assessment of response to therapy in advanced breast cancer. *Eur J Cancer* 1977, **13**, 89–94.
11. PETO R, PIKE MC, ARMITAGE P *et al.* Design and analysis of randomised clinical trials requiring prolonged observation of each patient. *Br J Cancer* 1977, **35**, 1–39.
12. KING RJB, REDGRAVE R, HAYWARD JL, MILLIS RR, RUBENS RD. The measurement of receptors for oestradiol and progesterone in human breast tumours. In: KING RJB, ed. *Steroid Receptor Assays in Breast Tumours; Methodological and Clinical Aspects.* Cardiff, Alpha Omega, 1979, 55–72.
13. VILLALON A, TATTERSALL M, FOX R, WOODS R. Hypercalcaemia after tamoxifen for breast cancer: a sign of tumour response. *Br Med J* 1979, 1329
14. MOURIDSEN HT, ELLEMANN K, MATTSSON W, PALSHOF T, DAEHNGELDT J, ROSE C. Therapeutic effect of tamoxifen versus tamoxifen combined with medroxyprogesterone acetate in advanced breast cancer in postmenopausal women. *Cancer Treat Rep* 1979, **63**, 171–175.
15. MOURIDSEN H, SALIMTSCHIK M, DOMBERNOWSKY P *et al.* Therapeutic effect of tamoxifen versus combined tamoxifen and diethylstilboestrol in advanced breast cancer in postmenopausal women. In: MOURIDSEN H, PALSHOF T, eds. *Breast Cancer: Experimental and Clinical Aspects.* Oxford, Pergamon Press, 107–110.