PAPERS AND ORIGINALS

Comparative Trial of Nafoxidine and Ethinyloestradiol in Advanced Breast Cancer: An E.O.R.T.C. Study

J. C. HEUSON, E. ENGELSMAN, J. BLONK-VAN DER WIJST, H. MAASS, A. DROCHMANS, J. MICHEL, H. NOWAKOWSKI, A. GORINS

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Summary

A randomized clinical trial of nafoxidine, a non-steroidal oestrogen antagonist, and ethinyloestradiol in postmenopausal patients with advanced breast cancer produced objective remissions in 31% of 49 women receiving nafoxidine and in 14% of 49 receiving ethinyloestradiol. The difference in remission rates was almost significant ($0.05 < P < 0.10$). Life-threatening complications were more frequent with ethinyloestradiol than with nafoxidine but the latter produced specific toxic reactions on skin and hair that may limit its practical usefulness. Synthetic oestrogen antagonists may occupy a privileged place in the treatment of breast cancer, and other representatives of this new class of compounds should be accurately assessed in randomized clinical trials.

Department of Internal Medicine and Clinical Investigation,
Institut Jules Bordet, Brussels, Belgium

J. C. HEUSON, M.D.

Department of Internal Medicine, Netherlands Cancer Institute,
Antoni van Leeuwenhoek Ziekenhuis, Amsterdam, The Netherlands

E. ENGELSMAN, M.D.

Rotterdam Radio-Therapeutisch Instituut, Rotterdam, The Netherlands

J. BLONK-VAN DER WIJST, M.D.

Universitäts Krankenhaus, Hamburg, Germany

H. MAASS, M.D.
H. NOWAKOWSKI, M.D.

Akademisch Ziekenhuis Sint-Rafaël, Leuven, Belgium

A. DROCHMANS, M.D.

Institut Médical des Mutualités Socialistes, La Hestre, Belgium

J. MICHEL, M.D.

Hôpital Necker, Paris, France

A. GORINS, M.D.

Introduction

Nafoxidine hydrochloride is a non-steroidal oestrogen antagonist. It inhibits the oestradiol-induced increase of uterine weight in rats which have undergone oophorectomy. Yet when given alone to these animals it produces a weak uterotrophic effect of its own.¹ It prevents oestradiol retention in the uterus, both in vivo and in vitro.²⁻³ These effects are thought to be mediated through the operation of the tissue-specific oestrogen receptors. Oestrogens first bind to the cytoplasmic receptors, and the resulting complex is then translocated into the cell nucleus where it triggers various metabolic reactions.⁴ Nafoxidine, like other antioestrogens, produces a similar sequence of events, but with a much lower potency.⁵⁻⁷ Recent data suggest that nafoxidine may operate in different ways: it displaced for protracted periods the receptors from the cytoplasm into the nucleus, thereby producing both antioestrogenic and weak oestrogenic effects.⁸ Moreover, nafoxidine has a biphasic action at the molecular level: at low concentrations it induces translocation of the nafoxidine-receptor complex into the nucleus, but at higher concentrations it inhibits this process as well as the translocation of the oestradiol-receptor complex. This inhibition might account for both its "antioestrogenic" and its "autoinhibitory" effects.⁹

Nafoxidine also prevents oestradiol retention in vitro in the DMBA-induced, hormone-dependent, rat mammary carcinoma⁹ and in human breast cancers.¹⁰ Moreover, it has antitumour effects on the rat mammary carcinoma. It prevents tumour induction¹¹ and inhibits tumour growth.¹¹⁻¹² These effects probably result from the operation of the same mechanisms as those acting in the uterus since these tumours have been shown to contain oestrogen receptors.¹³

Such considerations led the E.O.R.T.C. Breast Cancer Co-operative Group to test nafoxidine in a preliminary clinical trial in advanced breast cancer.¹⁴ Objective remissions were obtained in eight out of 23 patients (35%) who received the drug. These encouraging results prompted the same group to compare the therapeutic efficacy and side effects of nafoxidine with those of ethinyloestradiol in a randomized trial; ethinyloestradiol is generally considered to be the most effective hormone for treating breast cancer in postmenopausal women.¹⁵ We present here the results of this comparative trial.

TABLE 1—Data on 98 Patients Treated

	Age (Years)				Years after Menopause				Disease-free Interval (Months)					Dominant Site of Lesions (No. of Patients)			Previous Hormone or Cytotoxic Treatment (No. of Patients)
	No. of Patients	Mean	Median	Range	No. of Patients	Mean	Median	Range	No. of Patients	Mean	Median	Range	No. with No Interval*	Soft Tissues	Osseous	Visceral	
Nafoxidine	49	63	63	41-85	46	14	14	3-39	38	41	24	2-170	10	16	20	13	10/49
Ethinylestradiol	49	65	64	45-89	46	15	13	2-41	36	40	20	1-276	11	14	15	20	7/49

*Primary inoperable or already disseminated.

Patients and Methods

All the patients were women with inoperable, recurrent, or metastatic carcinoma of the breast. Proof on biopsy of recurrent or metastatic disease was obtained in most cases. When tumour tissue was not accessible for biopsy histopathological confirmation of the original malignancy was always secured. Any patient with a second cancer that could be confused with breast carcinoma was excluded from the study.

All patients were at least two years past their menopause, either natural or surgical. None had undergone castration, adrenalectomy, or hypophysectomy as a treatment for breast cancer before the study. Seventeen patients (see table I) had received previous hormonal or cytotoxic therapy or both, but all such therapy had been discontinued at least six weeks before the trial started, and no lesion had regressed in the meantime. No patient had received hormonal implants within two years of the study. The use of drugs which depressed hypothalamic activity was discouraged to avoid possible stimulation of prolactin secretion.¹⁶ X rays were given when necessary to localized lesions which caused a high risk to the patient of complications such as bone fracture or spinal cord compression. The lesions so treated and those nearby them which received significant irradiation were not used as criteria of response to hormonal therapy.

A prerequisite for admission of patients into the study was the presence of objective criteria for assessing response to treatment. Pleural effusion was not accepted as a criterion. Patients with central nervous system or "massive" liver involvement (more than a third of liver tissue replaced by tumour) were not admitted to the trial because they are notoriously resistant to endocrine treatments. Moribund patients were also excluded.

ASSESSMENT OF PATIENT'S RESPONSES

Initially all patients were given a thorough clinical examination, with x-ray examinations of the chest and skeleton and routine haematological and blood chemistry assessments. The soft-tissue lesions were measured with a caliper and photographed whenever possible. An isotopic liver scintigram was obtained in cases with suspected liver involvement. During treatment all the initial studies were repeated every six weeks until the response to treatment could be assessed.

Hormonal treatment was given for at least six weeks unless major intolerance occurred. Nafoxidine (U-11, 100A, Upjohn (1-{2-[p-(3,4-dihydro-6-methoxy-2-phenyl-1-naphthyl) phenoxy]-ethyl { -pyrrolidine hydrochloride)} 60 mg three times a day was given by mouth. Ethinylestradiol 1 mg three times a day was given by mouth. After six weeks the drugs were continued if there was objective remission or discontinued if the disease had progressed. When lesions were unchanged treatment was continued for another six weeks.

Objective remission was defined as a measurable decrease in the size of more than 50% of all non-osseous lesions provided the lesions, if present, had remained static. Recalcification of lytic bone lesions or disappearance of osteoblastic lesions was also interpreted as evidence of objective remission if these changes, when combined with a decrease in the size of other deposits, represented regression of at least 50% of all known lesions. When these criteria were not fulfilled after three months of treatment we considered that treatment had failed. We also considered that treatment had failed if there was progression of any lesion, regardless of its size or the response of other lesions; treatment was interrupted because of drug intolerance; the patient was lost to follow-up; or the patient died before response could be assessed. Patients who died within two weeks of the start of treatment were discarded from the trial, unless death was due to drug-related toxicity.

The patients' responses were provisionally assessed by the doctor in charge who took the decision to continue or discontinue treatment. For final assessment all the patient's records, including x-ray pictures, were reviewed completely by two independent physicians.

STRATIFICATION AND RANDOMIZATION

Patients were stratified according to the dominant site of lesions—soft tissues (breast, skin, subcutaneous tissues and muscles, and superficial lymph nodes), bones, or viscera (neoplastic pleural effusions, intrathoracic lymph nodes, other intrathoracic viscera, liver, and other intra-abdominal tissues). When multiple sites were involved a patient was classified in the category associated with the worst prognosis, and this was called the dominant site. The order of increasing gravity was: soft tissue, bone, and viscera.

The two treatments were randomized within each centre and within each category of dominant site. Numbered sets of sealed envelopes containing randomization forms prepared by the E.O.R.T.C. co-ordinating office were used.

Statistical Basis.—The number of patients required for the study was calculated on the basis of the following assumptions: the response rate to ethinylestradiol would be 20%; the response rate to nafoxidine would be 40%; and $\alpha = 0.05$; $\beta = 0.75$ —that is, the chances of showing the assumed difference 40 v. 20% at the $P = 0.05$ level are 3 out of 4. The calculation yielded: $2n = 130$ —that is, 65 patients in each treatment group.

Results

After review of all patients' records and exclusion of cases not conforming to the protocol each treatment group comprised 49 patients. The groups were similar (table I).

Numbers Available for Assessment.—In the nafoxidine group 45 patients received treatment for long enough to permit clearcut assessment of response by the protocol criteria. Treatment was interrupted prematurely in four patients, who were thus classified as failures; one was lost to follow-up, while the other three suffered from complications ascribed to drug toxicity—hypercalcaemia (one case), digestive intolerance (one), and liver toxicity (one). In the ethinylestradiol group 39 patients were available for definite assessment of response by the protocol criteria. Treatment was stopped prematurely in 10 patients, who were thus classified as failures; two were lost to follow-up, while the others developed complications ascribed to drug toxicity (hypercalcaemia (two cases), intractable digestive intolerance (four), uncontrolled fluid retention (one), and acute dyspnoea (one)).

Objective remissions were obtained in 15 out of 49 (31%) patients receiving nafoxidine and seven out of 49 (14%) receiving ethinylestradiol. This difference in response rate fell short of statistical significance at the 0.05 level ($\chi^2 = 2.872$; $0.05 < P < 0.10$). Previous hormonal treatment (excluding oestrogens or anti-oestrogens) or cytotoxic chemotherapy, or both, seemed not to decrease the chance of response, at least to nafoxidine. Thus, in patients who had been so treated objective remissions were obtained in three out of 10 receiving nafoxidine and in none out of seven receiving ethinylestradiol.

Prognostic Factors.—An analysis of the distribution of responses in relation to factors of prognostic significance in the treatment of advanced breast cancer¹⁷ failed to disclose obvious trends in either group (table II). The response rate to a given treatment was similar in all categories of menopausal age, disease-free interval, dominant site of lesions, and number of sites involved. Recalcification of bone lytic lesions occurred less often with both nafoxidine and ethinylestradiol than regression of soft tissue or visceral lesions but even by pooling the results of the two treatments the difference was not statistically significant ($\chi^2 = 3.05$; $0.05 < P < 0.10$).

Side Effects.—Side effects of nafoxidine consisted mainly of ichthyosis (11 cases) which increased with duration of treatment. Though non-pruriginous this skin change was sometimes extremely severe and made it difficult to pursue the treatment. Phototoxic reaction of the skin, without significant burn, occurred in most cases on exposure, even indirect, to sunlight. Partial loss of hair was recorded in six patients. Other complications were nausea and vomiting (mild in two

TABLE II—Numbers of Objective Remissions and Remission Ratios according to Prognostic Factors

	Nafoxidine		Ethinylestradiol	
	No. with Remission/ Total No.	Ratio	No. with Remission/ Total No.	Ratio
Total no. of remissions	15/49	0.31	7/49	0.14
Years after menopause:				
2-5	2/5	0.40	2/8	0.25
6-10	2/12	0.17	1/10	0.10
>10	11/31	0.36	4/29	0.14
Unknown	0/1	0.00	0/2	0.00
Free interval (months):				
Nil*	2/10	0.20	2/11	0.18
<24	8/20	0.40	3/20	0.15
24-48	2/8	0.25	0/9	0.00
>48	3/10	0.30	1/6	0.17
Unknown	0/1	0.00	1/3	0.33
Dominant sites of lesions:				
Soft tissues	5/16	0.31	3/14	0.21
Osseous	7/20	0.35	0/15	0.00
Visceral	3/13	0.23	4/20	0.20
No. of sites involved†:				
1	10/31	0.32	5/32	0.16
2	5/15	0.33	1/13	0.08
3	0/3	0.00	1/4	0.25
Regression in individual sites:				
Soft tissues	9/32	0.28	5/29	0.17
Bones	4/25	0.16	0/21	0.00
Viscera	3/13	0.23	4/20	0.20

*Primary inoperable or already disseminated.

†Soft tissues, osseous, or visceral sites.

cases, severe in one), hypercalcaemia (one case), liver toxicity characterized by raised serum transaminase levels (one), bilateral thrombophlebitis of both legs without previous history of thrombotic disease (one), and mild thrombocytopenia in a patient with bone marrow involvement (one). These complications led to discontinuation of treatment in three cases. The side effects of ethinylestradiol were nausea and vomiting (mild in one case, severe in four cases), hypercalcaemia (three cases), uncontrolled fluid retention (one), and acute dyspnoea (one). In eight cases treatment had to be stopped because of these complications.

Discussion

These results confirm our finding that nafoxidine is effective in the treatment of postmenopausal patients with advanced breast cancer.¹⁴ The total experience of the E.O.R.T.C. Group in our previous¹⁴ and two present trials (see Engelsman *et al.*,¹⁸ this issue) yields a rate of nafoxidine-induced objective remissions of 28% (30 remissions out of 108 patients treated). This rate is almost identical to that (33%) recently reported by Bloom and Boesen.¹⁹

Both treatment groups were similar, which indicated that no significant bias occurred during the randomization process. Though nafoxidine yielded a distinctly higher remission rate than ethinylestradiol the difference fell short of statistical significance and, therefore, was merely suggestive of nafoxidine's higher efficacy. Nafoxidine's apparent superiority may have been due, at least in part, to there being fewer premature interruptions of treatment on nafoxidine than on ethinylestradiol. Since most interruptions resulted from major drug intolerance, however, this explanation would leave intact the practical

superiority of nafoxidine though it is likely to level the biological therapeutic efficacy of the two drugs. Remission rates on either drug did not seem influenced by factors reported to be of prognostic significance in the treatment of advanced breast cancer,¹⁷ but this may have been due to the small numbers of patients.

Apart from the eight cases of major intolerance ethinylestradiol produced no significant untoward effects. In contrast, nafoxidine produced fewer life-threatening reactions but produced very specific side effects. Ichthyosis was sometimes severe enough to make it difficult to pursue treatment. Partial hair loss was a significant complaint. Phototoxicity of the skin, which occurred in nearly all patients on mild or even indirect exposure to sunlight was inconvenient during the summer.

As an oestrogen antagonist nafoxidine is one of a new class of compounds which have proved to be active in the treatment of breast cancer. Our results suggest that in this disease it is one of the most effective hormone-related drugs though its practical usefulness is limited by its toxicity on skin and hair. Other oestrogen antagonists such as tamoxifen (I.C.I. 46474) have recently been reported to be therapeutically active in breast cancer and devoid of major side effects.²⁰⁻²¹ It is important to assess the exact therapeutic value of these compounds in controlled clinical trials.

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