J. steroid Biochem. Vol. 36, No. 3, pp. 237–238, 1990
Printed in Great Britain. All rights reserved

0022-4731/90 $3.00 + 0.00
Copyright © 1990 Pergamon Press plc

PHASE II CLINICAL STUDY OF HIGH-DOSE TOREMIFENE IN PATIENTS WITH ADVANCED BREAST CANCER

H. MODIG,[1]* S. BORGSTRÖM,[2] I. NILSSON[2] and G. WESTMAN[3]
Departments of Oncology, [1]Umeå University Hospital, [2]Malmö General Hospital and [3]Örebro Regional Hospital, Sweden

Summary—Thirteen postmenopausal women with advanced local or metastatic breast cancer were treated with the antiestrogen toremifene at a daily dose of 200 mg. All patients had failed previous treatment with different types of endocrine therapy and/or cytotoxic drugs. Objective response was only seen in one patient. Treatment was usually well tolerated but in three cases the drug had to be withdrawn due to side effects.

INTRODUCTION

Using MCF-7 cells *in vitro* and DMBA-induced rat mammary carcinoma *in vivo*, a dose-dependent antitumor effect with toremifene has been shown. Toremifene also inhibits the growth of mouse uterine sarcoma resistant to tamoxifen treatment [1].

The aim of the present study was to investigate the effect of high-dose toremifene in patients with advanced breast cancer refractory to standard endocrine and cytotoxic therapy.

SUBJECTS AND METHODS

Thirteen postmenopausal women with locally advanced or metastatic breast cancer were entered into the study. All patients had failed previous therapy including first and second line endocrine treatment and/or cytotoxic drugs. The patients were required to have histologically verified mammary cancer, bidimensionally measurable disease, a Karnofsky index of at least 60, expected survival time of at least 3 months and positive or undetermined estrogen receptor status.

At the start of the treatment and every 4 weeks, clinical examination with assessment of all tumor sites was performed. Laboratory tests at entry and follow up included ESR, Hb, WBC, platelets, electrolytes, creatinine, ASAT, ALP, GT, protein in urine and blood glucose. Chest X-ray and bone scan were performed when necessary. UICC response criteria were used.

Toremifene dose was p.o. 200 mg daily and the treatment was continued until serious side effects were noted or until progression of the disease.

Patient characteristics are shown in Table 1.

RESULTS AND DISCUSSION

The treatment results are presented in Table 2. Only one objective response was noted. This patient had a soft tissue tumor and lymph node metastases and had previously failed on tamoxifen and MPA. No adverse effects were seen on peripheral blood, creatinine and electrolytes. The liver function tests were normal in all patients except one who had an increase in transaminases. These values were normalized after withdrawal of the drug. In two patients therapy had to be stopped due to severe nausea and two patients developed hematuria. These patients used analgesics containing acetylsalicylic acid and hematuria was probably not due to the toremifene treatment. Two patients experienced mild nausea. The treatment was usually well tolerated and the symptoms were reversible when the therapy was discontinued.

The patients in this study were usually heavily pretreated with endocrine therapy and cytotoxic drugs and they suffered from multiple lesions. This may explain the rather poor treatment result. The

Table 1. Patient characteristics

Total patients entered	13
Evaluable	13
Median age in years (range)	61 (39–74)
Median performance status (range)	80 (60–100)
Sites of metastatic disease	
Soft tissue	10
Lymph node	2
Lung-pleura	3
Bone	6
Liver	1
Brain	1
Estrogen receptor status	
Positive	8
Undetermined	5

Proceedings of the Toremifene Satellite Symposium held at the *UICC World Cancer Congress*, Budapest, Hungary, 1986.

*To whom correspondence should be addressed at: Department of Oncology, Umeå University Hospital, S-901 85 Umeå, Sweden.

Table 2. Clinical response and duration of treatment in months

CR	0/13	
PR	1/13	7+
NC	4/13	2[a], 2[b], 4[c], 4+
PD	8/13	2–4, 6+

[a]Treatment stopped due to increase of liver transaminases.
[b]Treatment stopped due to nausea.
[c]Progressive disease after 3 months.
CR: Complete Remission; PR: Partial Remission; NC: No Change; PD: Progressive Disease.

only responding patient had no prior cytotoxic treatment and limited disease in breast and lymph nodes.

High-dose toremifene should be investigated also as a second line endocrine therapy, because the preliminary results by Ebbs *et al.*[2] and Hindy *et al.*[3] indicate a better response rate in this indication.

REFERENCES

1. Kangas L., Nieminen A-L., Blanco G., Grönroos M., Kallio S., Karjalainen A., Perilä M., Södervall M. and Toivola R.: A new triphenylethylene compound, Fc-1157a. II. Antitumor effects. *Cancer Chemother. Pharmac.* **17** (1986) 109–113.
2. Ebbs S. R., Roberts J. V. and Baum M.: Alternative mechanism of action of "anti-oestrogens" in breast cancer. *Lancet* **ii** (1987) 621.
3. Hindy I., Juhos E., Szántó J. and Számel I.: Effect of high-dose toremifene in breast cancer patients. *14th UICC Int. Cancer Congr.*, Budapest, August 21–27, 1986. Karger, Budapest (1986) p. 553.