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# TOREMIFENE, A NEW ANTIESTROGENIC COMPOUND IN THE TREATMENT OF METASTATIC MAMMARY CANCER. A PHASE II STUDY

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**Summary**—Toremifene is a new antiestrogenic compound. Toremifene has definite antitumor effect in advanced breast cancer. The response rate in the present phase II study among postmenopausal women, mostly not pretreated with systemic therapy and with ER positive or not determined ER status in tumor tissue, was 11/23 (48%; 95% confidence interval 37–59%) including 6 complete responses. The toxicity profile was similar to that of tamoxifen. It is concluded that toremifene is at least as active as tamoxifen in advanced breast cancer and that a randomized study between these two antiestrogens is indicated.

## INTRODUCTION

Toremifene is an antiestrogenic antitumor substance. It binds to the estrogen receptors of the cytosol and can be translocated into the nucleus. A depletion of both cytosolic and nuclear receptors occur leading to the cessation of cell growth stimulated by estrogen and to the regression of the sensitive tumor. The antitumor effect of toremifene is specifically directed to estrogen-dependent tumors—cancers of the mammary gland and of the endometrium. The area of indication is based on the pharmacologic mode of action which resembles that of tamoxifen.

Animal toxicity and human phase I clinical studies have shown toremifene to be a safe and well tolerated substance. In breast cancer patients the hormonal effects of toremifene are quite similar to those of the currently used antiestrogen tamoxifen although toremifene seems to be slightly more potent [1, 2]. Of great interest, however, was the finding that toremifene, in contrast to tamoxifen, lowered the initially high estradiol levels [3]. Although the detailed nature of this phenomenon is unclear, it must be considered favourable in the treatment of estrogen-dependent cancers such as breast cancer.

The antiestrogenic effect of 60 mg of toremifene in the mucous membranes of the vagina resembles the antiestrogenic effect of about the same dose (68 mg) of tamoxifen [2]. Therefore a dose of 60 mg was chosen for this first phase II study to point out the possible antitumor effect.

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## PATIENTS AND METHODS

Twenty-four postmenopausal patients with histopathologically verified advanced breast cancer were included in the study; of these 23 were evaluable. One patient died from cardiac failure, probably caused by known pericardial metastases, 2 weeks after the start of treatment and has not been included in this analysis. Postmenopausality of the patients was defined as at least one year since the last menstruation or over 55 years of age if hysterectomy had been performed. Only patients with estrogen receptor positive tumor tissue or patients with undetermined receptor status were selected, i.e. patients with definitive ER poor receptor status in tumor tissue were excluded.

The mean age of the evaluable patients was 66 yr, ranging from 49 to 84 yr. Thirteen patients had ER positive tumor tissue while for 10 patients ER status was undetermined. Sixteen patients had lung and/or pleural metastases, 8 had soft tissue manifestations and 6 bone metastases. Five patients had more than one organ system involved. Three patients had received chemotherapy. Otherwise patients were previously untreated with regard to systemic therapy including adjuvant chemo- or hormone therapy.

ER was measured by a standard dextran-charcoal method with [$^3$H]estradiol as the ligand, essentially as recommended by the European Organization for Research on Treatment of Cancer [4]. Results of the ER assay were given as pmol/g cytosol protein. In breast cancer, values > 10 pmol/g were considered positive if the dissociation constant was satisfactory.

The quality of the receptor measurements was monitored by the inclusion of quality control samples in each run and by participation in the running EORTC European Quality Control Assessment of

Table 1. Main patient characteristics

| | |
|---|---|
| No. of patients | 24 |
| Early death, not drug related | 1 |
| Evaluable patients | 23 |
| Postmenopausal | 23 |
| Age, mean (yr, range) | 66 (49–84) |
| Performance status (ECOG), mean (range) | 1 (1–2) |
| ER positive (> 10 pmol/g protein) | 13 |
| mean (range) | 71 (11–500) |
| ER unknown | 10 |
| Disease free interval, mean, months (range) | 49 (0–119) |
| Pretreatment site of involvement | |
| Bone | 6 |
| Soft tissue | 8 |
| Visceral | 16 |
| >1 organ involved | 5 |
| Prior therapy | |
| Adjuvant chemotherapy | 2 |
| Chemotherapy for metastatic disease | 1 |
| Hormone (including adjuvant) therapy | 0 |

Steroid Receptor Assays, all giving fully satisfactory results.

Metastases were measurable or evaluable. Patients with brain metastases, leptomeningeal affection or osteoblastic disease as the only manifestation of the disease were excluded. Prior to the start of treatment and after every three months, patients had a medical and radiographic evaluation of response together with routine hematologic parameters. Criteria for response were those recommended by UICC [5].

The main patient characteristics have been summarized in Table 1.

## RESULTS

Response to the toremifene treatment has been presented in Table 2. The remission rate (complete and partial) was 48% (with 95% confidence intervals 37–59%). Median duration of remissions was 14 months for complete remissions with 3 patients still in complete remission 16, 24 and 28 months after the start of treatment. Two of these patients had multiple round lung metastases and one had a local relapse and pleural exudation. For partial remissions the median duration of remission was 15 months with 3 patients still in remission after 10, 17 and 19 months of treatment.

In general toremifene was well tolerated. One patient had diarrhea that subsided after 2 weeks cessation of treatment. She was then treated with tamoxifen. The diarrhea then returned, but could be controlled by moderate doses of diphenoxylate chloride. Hot flushes, similar to those observed on tamoxifen, were reported by about half of the patients. Moderate weight gain, 1–2 kg, was recorded in some patients.

Table 2. Response to treatment

| Response | No. of patients | Duration of response median, months (range) |
|---|---|---|
| Complete remission | 6 | 14 (9–28+) |
| Partial remission | 5 | 15 (9–19+) |
| No change | 6 | |
| Progressive disease | 6 | |

## DISCUSSION

The response rate to tamoxifen for patients selected on the same premises as the present protocol has been reported to be approximately 35% [6]. The response rate for toremifene is of the same magnitude. Any significant difference in efficacy will have to be solved by randomized studies including a large number of patients. Moreover, it would be a great interest to evaluate the efficacy of toremifene in tamoxifen resistant patients.

Toremifene was well tolerated and few side effects were observed. When present these were of gastrointestinal nature, moderate weight gain and hot flushes. The toxicity profile thus resembles that of tamoxifen.

In conclusion, toremifene definitely has antitumor effect in breast cancer with at least equivalent efficiency as tamoxifen with similar toxicity profile. Thus it feels warranted to compare the two antiestrogens in a randomized cross-over trial. However, it must be emphasized that this implies the inclusion of a substantial number of patients since only a small (10–15%) difference should be expected.

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