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# AMINOGLUTETHIMIDE AND ESTROGENIC STIMULATION BEFORE CHEMOTHERAPY FOR TREATMENT OF ADVANCED BREAST CANCER. PRELIMINARY RESULTS OF A PHASE II STUDY CONDUCTED BY THE E.O.R.T.C. BREAST CANCER COOPERATIVE GROUP

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**Summary**—While both endocrine therapy and chemotherapy are of proven value in the treatment of advanced breast cancer, the effects of combining these two methods or applying them consecutively have been relatively disappointing. This may be due to endocrine therapy suppressing cell division, in hormone-dependent tumors, whereas chemotherapy acts mainly on active-dividing cells. A trial protocol has therefore been devised which seeks to exploit the properties of both types of therapy. Oestrogen suppression is first obtained by aminoglutethimide (Orimeten®) plus hydrocortisone; after 2 weeks, ethinyloestradiol is given to induce cell division and followed 24 h later by a combination of 3 cytotoxic agents given intravenously. This pattern of therapy, repeated at regular intervals, appears to be producing favorable clinical results. A phase-III study is being started among patients with hormone-dependent advanced breast cancer.

## INTRODUCTION

As breast cancer responds both to endocrine therapy (ET) and chemotherapy (CT), empirical combinations of these two modalities have been proposed for palliation of advanced disease. To date, various associations of standard chemotherapeutic regimens and either endocrine ablative surgery or pharmacological doses of hormones or antihormones have been tested. This approach generally allows the clinician to achieve higher response rates for longer relapse-free periods than with either modality used singly. In spite of these interesting results, complete remissions (CR) remain relatively infrequent. Moreover, at least for highly hormone-dependent tumors, the benefits of combined treatment remain questionable. It seems to give no significant lengthening of survival compared to that of patients treated first by ET, then by CT given at the time of relapse. The lack of true synergism between ET and CT might be ascribable to their different and possibly mutually-exclusive mechanisms of action. The proliferative index of hormone-dependent tumors is decreased under ET, whereas cytotoxic drugs are known to kill cells predominantly engaged in the mitotic cycle.

New perspectives arose from recent experiments [1–3], showing that one brief estrogenic stimulus could transiently force quiescent hormone-dependent cells, chronically deprived of estrogens, to re-enter the mitotic cycle. This endocrine manipulation, "estrogenic recruitment", might amplify the effects of cytotoxic drugs and eradicate resting progenitor neoplastic cells in oestrogen receptor positive tumors. Furthermore, new pharmaceutical means for blocking the endogenous production of estrogens, i.e. the combination of aminoglutethimide (AGL) + hydrocortisone (HC) are now available [4], enabling a therapeutic regimen to be based on the concept of estrogenic recruitment. This paper reports the preliminary results of a hopefully synergistic hormono–chemotherapeutic combination tested in a phase-II study by the E.O.R.T.C. Breast Cancer Cooperative Group.

## EXPERIMENTAL

### *Patients and methods*

All patients included in this trial had advanced breast cancer, histologically proved, with evaluable and/or measurable lesions. None of them had received prior systemic antineoplastic therapy. Response to treatment was evaluated according to standard UICC criteria [5] and submitted to extramural review.

The endocrine part of the therapeutic regimen aimed to achieve a deep and prolonged estrogenic suppression. All patients received a continuous treatment with aminoglutethimide (1.0 g/d) and hydrocortisone (40 mg/d). Since these drugs are not capable of adequately suppressing ovarian production of steroidal sex hormones, premenopausal women also

Table 1. Characteristics of 47 evaluable patients

| | |
|---|---|
| Age | median 58 years; range 36–69 years |
| Performance status (WHO) | median 0.6; range 0–3 |
| Prior therapy | surgery 30 patients; radiotherapy 25 patients |
| Menopausal status | pre 12 patients; post 35 patients |
| Dominant metastatic site | soft tissue 10 patients (21%);<br>bone 12 patients (26%);<br>viscera 25 patients (53%). |

underwent surgical castration. Two weeks after initiating the endocrine treatment, cyclical chemotherapy was started with a 3-drug combination of 5-fluorouracil (5-FU) adriamycin (ADM) and cyclophosphamide (CPA). These drugs were given every 3 weeks (5 FU 500 mg/m$^2$; ADM 50 mg/m$^2$; CPA 500 mg/m$^2$) exactly 24 h after the oral administration of ethinylestradiol (50 $\mu$g), the hormonal recruiting agent. After 11 cycles, ADM was replaced by methotrexate (50 mg/m$^2$ i.v.) in order to avoid ADM-induced cumulative cardiotoxicity and the treatment was pursued until the disease progressed.

## PRELIMINARY RESULTS

By August 1983, 67 eligible patients had been included in the study. Eleven cases, recently registered by the E.O.R.T.C. Data Center, have not yet been evaluated because their treatment had only just begun. Nine cases were found to be inevaluable for various reasons, including early death not related to treatment or to disease progression (1 patient), protocol violation by giving an inadequate treatment (2 patients), treatment refusal by the patient (2 patients) and withdrawal of treatment because of excessive toxicity, mainly intolerance to aminoglutethimide (4 patients). The characteristics of the 47 fully evaluable cases are listed in Table 1. Overall response and response rates according to several putative prognostic factors are detailed in Tables 2 and 3, respectively.

Table 2. Overall response in 47 patients

| Response | No. of patients | (%) |
|---|---|---|
| Complete remission (CR) | 17 | (36) |
| Partial remission (PR) | 18 | (38) |
| Stable disease (NC) | 1 | (2) |
| Failure by progression (PD) | 11 | (24) |

The median duration of remission and survival has not yet been reached at the time of evaluation. Side-effects of chemotherapy consisted mainly of leucopenia with a median nadir of 2600/mm$^3$ (range 1000–3800) occurring on day 19, gastrointestinal disturbances (88% of patients) and alopecia (77% of patients). Aminoglutethimide-induced drowsiness (35% of patients) and skin rashes (20% of patients) occurred mainly during the first 2 weeks of treatment and were generally mild and short-lived.

## PRELIMINARY CONCLUSIONS

The present regimen seems highly effective for inducing remissions in advanced breast cancer. The complete remission rate of 36% obtained here compares favorably with the average 20% CR generally achieved with the best empirical hormono-chemotherapeutic combinations [7, 8]. It should be stressed that most patients in this series were unselected cases with regard to the presumed degree of hormone-dependency of their tumors. The latter might even be rather low, as suggested by the high proportion of patients with visceral metastases. In view of these results, a phase III trial aiming to validate the concept of estrogenic recruitment has now been activated. It is restricted to oestrogen-receptor-positive cases and patients are randomized to receive either ethinylestradiol or placebo, according to a double-blind design, before starting chemotherapy.

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Table 3. Response according to prognostic factors

| | No. of patients | Cr (%) | CR + PR (%) |
|---|---|---|---|
| *Dominant metastatic site* | | | |
| Soft tissue | 10 | 4 (40) | 8 (80) |
| Bone | 12 | 6 (50) | 9 (75) |
| Viscera | 25 | 7 (28) | 18 (72) |
| *Menopausal status* | | | |
| Premenopausal | 12 | 5 (42) | 9 (75) |
| Postmenopausal | 35 | 12 (34) | 26 (74) |
| *Estrogen receptors** | | | |
| ER $\geq$ 30 fmol/mg protein | 7 | 3 (43) | 6 (86) |
| ER < 30 fmol/mg protein | 9 | 3 (33) | 5 (55) |
| ER unknown | 31 | 11 (35) | 24 (77) |

*Assays performed according to the standardized dextran-coated charcoal method adopted by the EORTC Breast Cancer Cooperative Group [6].

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