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ASSESSMENT OF ESTROGENIC RECRUITMENT BEFORE CHEMOTHERAPY IN ADVANCED BREAST CANCER: PRELIMINARY RESULTS OF A DOUBLE-BLIND RANDOMIZED STUDY OF THE EORTC BREAST CANCER COOPERATIVE GROUP

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Summary—We investigated whether estrogenic recruitment could enhance the antitumor effect of chemotherapy in 165 patients with advanced breast cancer, presumably sensitive to hormonal treatments (ER+ and/or PgR+ lesions). The therapeutic regimen consisted of: (a) estrogenic suppression by aminoglutethimide 1 g/day + hydrocortisone 40 mg/day; surgical castration in premenopausal patients only; (b) FAC (5FU 500 mg/m^2; ADM 50 mg/m^2; CPA 500 mg/m^2) for 3 weeks; (c) following randomization, exactly 24 h prior to chemotherapy, patients had to take 1 tablet of either placebo (PL) or 50 μg ethinylestradiol (EE2). Tolerance, responses, time to progression and median survival were identical in both groups. Thus, EE2 before chemotherapy did not contribute to the efficacy of this particular therapeutic regimen, which yielded an overall response rate of 64%. We conclude that the validity of the hormonal recruitment concept has not yet been established in clinical practice, so that this approach remains experimental.

INTRODUCTION

Both hormonal therapy (HT) and chemotherapy (CT) are of established value in the treatment of breast cancer. Their efficacy, their spectra of activity, their mechanisms of antitumor action and their side-effects are very different, so that empirical combinations of these two modalities have been proposed for palliation of advanced disease, or for adjuvant purposes. 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, it appears that the benefit at best is simply additive [1].

In fact, HT and CT may sometimes interact in a negative way. Endocrine manoeuvers, when effective, seem to reduce the proliferative index in hormone-sensitive tumors, leading to the death of the most hormone-dependent part of the neoplastic cell population, and putting the remaining part in a quiescent, non-dividing status. On the other hand, cytotoxic drugs are non-specific cell poisons, which predominantly kill the cells engaged in the mitotic cycle, several agents being more active during one phase or another of this cycle. Thus, the lack of true synergism between HT and CT on neoplastic cells may be ascribed to their different, possibly mutually exclusive, mechanisms of action. Moreover, one possible mechanism of resistance in chemosensitive tumors may operate through the temporary reversible shift of one part of the cell population (theoretically, one single cell may suffice) to the resting G_0 phase, in which they are protected against cytotoxic agents. The latter concept led to a new strategy, in which the growth-promoting properties of hormones, and especially estrogens, were exploited to force quiescent cells to enter into division, thereby rendering them vulnerable to chemotherapy.

In light of experimental data accumulated in *in vitro* and *in vivo* experiments [2–8], showing that estrogens might enhance the killing effect of antineoplastic drugs, we designed a therapeutic regimen based on the concept of estrogenic

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recruitment. This regimen was found highly effective, without undue toxicity, in a pilot study conducted by the EORTC Breast Cancer Cooperative Group [9, 10]. We present here the preliminary results of the subsequent phase III trial, in which the contribution of estrogenic stimulation was evaluated.

PATIENTS AND TREATMENT

The endocrine part of the treatment aimed at achieving a deep and prolonged estrogenic suppression. All patients received continuous treatment with aminoglutethimide (1.0 g/day) and hydrocortisone (40 mg/day), and premenopausal women also underwent surgical castration. Two weeks after initiating the endocrine treatment, cyclical chemotherapy was started with a 3-drug combination of 5-fluorouracil (5-FU 500 mg/m^2), adriamycin (ADM 50 mg/m^2) and cyclophosphamide (CPA 500 mg/m^2) (FAC regimen). In a preliminary phase II trial accruing patients with advanced disease, these drugs were given i.v. every 3 weeks exactly 24 h after the oral administration of ethinylestradiol (EE2; 50 μg), the recruiting agent. This regimen induced a high proportion of remissions (75%), of which about half were complete, without causing any unexpected toxicity [9]. In the present randomized study, only patients with presumably hormone-dependant (ER+ and/or PgR+) metastatic disease were included. They received in double-blind either a placebo (PL) or EE2 24 h before chemotherapy.

After 11 cycles of FAC, ADM was replaced by methotrexate (50 mg/m^2) in order to avoid the ADM-induced cumulative cardiotoxicity, and the treatment was pursued until the disease eventually progressed. In patients having a complete remission (CR) maintained after 24 months, chemotherapy was stopped, whereas intake of AGL + HC was maintained. All patients were followed regularly, and response was evaluated according to the UICC criteria at 3-month intervals.

RESULTS

Between September 1983 and July 1987, 165 patients were treated according to the protocol. The list of participants and the results are given in Tables 1 and 2. Responses, presently available after extramural review of 125 cases, were identical (CR + PR 64%) in the PL and EE2 groups, as were median times to progression (95 weeks) and median survival durations (112 weeks). Only performance status (PS) and menopausal status (MS) seemed to the influence response (CR + PR): 22% + 45% if PS = 0 vs 5% + 54% if PS = 1 to 2; 24% + 52% if pre- vs 10% + 48% if postmenopause. Side effects were mainly attributable to chemotherapy (GI disturbances, alopecia, leucopenia), and were identical in the two arms of the study.

DISCUSSION

No difference was observed, either in response rates, survival or tolerance, between the two arms of this trial. We thus conclude that low dose EE2 before FAC does not modify the efficacy of the FAC regimen. Nevertheless, the combination of deep hormonal suppression (AG + HC, and ovariectomy in premenopausal patients) with the FAC regimen yielded a high remission rate, comparable to that expected for additive hormonochemotherapeutic associations.

Similar studies, based on the concept of endocrine recruitment, but using different therapy schedules were conducted by other groups either as pilot or comparative randomized trials. Their designs include either estrogen alone (DES) or tamoxifen administration followed by

Table 1. EORTC 10835—phase III study comparing double-blind placebo vs estrogenic recruitment before chemotherapy in advanced disease; participants in the study

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Table 2. EORTC 10835—phase III study comparing double-blind a placebo (PL) vs ethinylestradiol (EE2) before chemotherapy; response by treatment and by prognostic factors (123 cases reviewed)

	Patient No.	CR (%)	CR + PR (%)	SD (%)	Fail (%)	Comparison *P*
Treatment						
EE2	62	11	63	25	12	NS
PL	61	16	63	20	17	
Menopause						
Pre	34	24	76	18	6	0.01
Post	89	10	58	25	17	
Age (yr)						
<50	35	23	74	17	9	
50–59	41	10	59	24	17	NS
⩾60	47	11	60	25	15	
Karnofsky (%)						
100	58	22	67	26	7	
80–90	42	7	60	21	19	0.007
<80	19	0	58	21	21	
Chemo (adj.)						
No	102	16	65	22	13	NS
Yes	21	5	57	24	19	
Metas. dom.						
Soft	20	30	75	15	10	
Bone	37	5	57	35	8	NS
Visc.	66	14	64	18	18	
ER level (fmol/mg)						
<30	34	15	56	29	15	
30–100	41	20	69	17	15	NS
>100	39	8	62	25	13	

CR = complete remission; PR = part remission.

estrogenic rescue, or even alternation of estrogen and progestin [11–17].

Let us mention that Lipton *et al.* [18] used a strategy comparable to that of the EORTC Breast Cancer Cooperative Group, i.e. hormonal depletion followed by estrogenic recruitment preceding chemotherapy. Accrual was restricted to postmenopausal women, who were treated with aminoglutethimide and hydrocortisone continuously; cyclic chemotherapy with the FAC combination was repeated every 3 weeks. Patients were randomized to receive (in double-blind) either a placebo (arm A) or estradiol (2 × 2 mg/day, arm B) during 3 days before the FAC injection. Among 28 evaluable cases, 5 remissions occurred in arm A (12 patients) and 5 also in arm B (16 patients). It should be noticed that, in addition to these relatively low response rates, tumor flares were observed in arm B only, suggesting that chemotherapy given after 3 days of hormonal administration was unable to counteract the stimulating effects of estrogens.

Finally, in the randomized studies of Conte *et al.* [13–15], which also aimed at testing the concept of estrogenic recruitment, DES was used as priming before FAC or FEC. They did not record any benefit from the hormonal manipulation, which seemed to be also responsible for a greater hematologic toxicity. The latter, however, might also be explained by the asymmetrical design of the study, as far as chemotherapy is concerned: all cytotoxic drugs were given on day 1 in the control arm (without hormonal stimulation), whereas they were given on days 1 and 8 in the recruitment arm. This asymmetry obviously contributed to obscuring the interpretation of the negative results of the study, so that another trial, conducted by the same group, with identical chemotherapy schedules in both control and recruitment arms is ongoing.

Analysis of the available literature data on hormonal recruitment trials in either breast cancer or prostatic carcinoma does not provide, at present, any indication that such manipulation is clinically useful. In our study, a small dose of EE2 given 24 h before chemotherapy was without any detectable effect. In trials using a longer stimulation period before chemotherapy, both in breast and prostatic cancers, dangerous flares were observed [18–21] and even a survival disadvantage was reported for androgenic priming in prostatic cancer [20], indicating that chemotherapy had probably been given too late, becoming unable to block the hormonally-induced stimulation of tumor growth. Similar flares were also reported, two decades ago, when

androgens were used for several days before radiotherapy with i.v. radiophosphorus, given for palliative therapy of prostatic cancer with bone metastases: patients complained of enhanced bone pain, requiring opiates, acid phosphatases rose and several cases of acute spinal cord compressions were even described [22–24]. This is in agreement with cell kinetic data showing that only a few hours are needed for resting cells to enter into division, and that the whole duration of the cycle is about 24 h. We might even assume that chemotherapy should be preferably started immediately, together with the administration of the recruiting agent.

We conclude that the validity of the hormonal recruitment concept has not yet been established in clinical practice, so that this approach remains strictly experimental. In standard practice, outside the context of well designed trials, chemotherapy and endocrine treatments should, in general, be used singly, the therapeutic choice between these modalities being conditioned by all available prognostic factors currently used to evaluate the hormone-dependence of the tumor and its aggressiveness.

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