Eur J Cancer Clin Oncol, Vol. 23, No. 7, pp. 897–900, 1987.
Printed in Great Britain

0277–5379/87$3.00+0.00
Pergamon Journals Ltd.

Perspectives and Commentaries

Stimulation of Breast Cancer with Estrogens: How Much Clinical Value?

NANCY E. DAVIDSON* and MARC E. LIPPMAN†

**Johns Hopkins Oncology Center, 600 North Wolfe Street, Baltimore, MD 21205 and †Medical Breast Cancer Section, National Cancer Institute, National Institutes of Health, Bethesda, MD, 20892, U.S.A.*

(A COMMENT ON: Kiss R, Paridaens R, LeClercq G, Danguy A. Sensitivity of the hormone dependent MXT-mouse mammary carcinoma to estradiol during tumoral growth. An autoradiographic study. *Eur J Cancer Clin Oncol* 1986, **22**, 849–856.)

BREAST cancer treatment has been the subject of intense investigation and substantial progress has been made using both hormonal and chemotherapeutic approaches. However, current results of treatment of advanced disease have suggested a plateauing of success such that 40–70% of patients will respond to first-line multi-drug regimens with a median survival of 12–24 months. Similarly the response rate to endocrine therapy remains at best about 35% in an unselected patient population.

This therapeutic impasse has led to the investigation of combined chemoendocrine therapy as one means of improving treatment results. The theoretical rationale for a combined approach in a heterogeneous disease like breast cancer is clear. The 2 treatment modalities appear to exert their antineoplastic effects by different mechanisms of action. Therefore combined therapy may be anticipated to have an additive or perhaps synergistic effect although negative interactions are also possible. Furthermore their different toxicities should make it possible to administer together 2 therapies of proven efficacy in an intensive fashion without undue side effects.

Unfortunately a number of possible objections may be raised as well. First, an additive effect may be less rewarding than expected as an improvement in response rate of 10–20% at best may be expected with combined therapy assuming no synergism. Second, there is no evidence that combined therapy will be more effective than sequential therapy. Third, a number of potential detrimental interactions between the 2 approaches can be identified. Foremost amongst these is the possibility that endocrine intervention may perturb cell cycle kinetics so as to render cells less responsive to chemotherapy. Treatment of hormone-dependent breast cancer cells *in vitro* with antiestrogens like tamoxifen induces a reversible G1 arrest while many commonly-used cytotoxic drugs are active against actively dividing cells. Thus any endocrine therapy which might transiently slow the growth of breast cancer cells might paradoxically protect those cells from the effects of chemotherapeutic agents [1].

A number of clinical trials using combined endocrine and chemotherapy in breast cancer have been performed. Several trials examined the addition of chemotherapy to oophorectomy in premenopausal women with metastatic breast cancer. Overall they suggest that improved response rate and duration are achieved wth the combined approach but no clear evidence of enhanced overall survival has emerged. Other trials examining the addition of androgens, progestins, or diethylstilbestrol to combination chemotherapy for treatment of advanced disease have been equally unrewarding. Most recent trials have focused on the use of tamoxifen with multiagent chemotherapeutic regimens either concurrently or sequentially. Generally, the overall response rate and time to progression are increased but a convincing improvement in survival has been demonstrated only infrequently. It is noteworthy

Accepted 5 November 1986.

that similar conclusions have been drawn from studies of chemoendocrine therapy as an adjuvant treatment for early breast cancer. An increase in relapse-free survival is often seen with the combined approaches but overall survival remains nearly the same. In addition, combined data from the adjuvant literature suggest that recipients of combined modality therapy may actually do worse than their counterparts treated with a single approach, providing indirect evidence for the possible negative interaction between endocrine and chemotherapy mentioned above (for review see [2]).

Given the disappointing nature of these results, a second approach to combined therapy has been under investigation, that of hormonal priming. Here endocrine therapy is administered in a pulse fashion to induce a synchronously stimulated wave of tumor cell proliferation, thus rendering the cells more susceptible to the cytotoxic effects of chemotherapeutic agents. Presumably such a synchronization or recruitment approach would not affect the major sites of drug toxicity, bone marrow and gastrointestinal tract, which are not estrogen-responsive tissues, and these sites would therefore be spared additional toxicity.

Support for this approach may be drawn from several cell culture and animal studies. Weichselbaum *et al.* [3] showed increased sensitivity of estrogen receptor-positive MCF-7 cells to cytosine arabinoside if their growth rate was increased by administration of 17β-estradiol in physiological concentrations. Pretreatment with a pharmacological dose of estrogen decreased cell growth rate and sensitivity to cytosine arabinoside. Other studies with MCF-7 cells have shown that tamoxifen-induced estrogen deprivation followed by physiological estrogen replacement induced a marked increase in breast cancer cell growth fraction [4]. In addition, Kiss and colleagues have recently reported that the injection of a single dose of 17β-estradiol into castrated mice bearing MXT transplantable mammary tumors resulted in increased thymidine labeling index in the tumors. This enhanced sensitivity to estradiol and the level of tumor estrogen receptor content were constant during MXT tumor growth up to 6 weeks after implantation [5]. Similarly, an increased thymidine labeling index in the tumor cells of patients with skin or soft tissue metastases who have been exposed briefly to physiological doses of estrogen and progesterone has been observed [6].

Several trials have addressed the efficacy of this approach as treatment for metastatic breast cancer. An early phase-II trial of tamoxifen–Premarin synchronization followed by methotrexate and 5-fluorouracil showed an overall response rate of 62% and a complete response rate of 37% in 57 evaluable patients. The majority of these patients had non-visceral sites of disease and had received little or no prior therapy for treatment of advanced disease [7]. Unfortunately these results were not duplicated in a second trial using an identical regimen but in more heavily pretreated patients; the overall response rate in 30 such patients was less than 10% [8]. The only randomized trial to address this approach employed a regimen of cyclophosphamide and doxorubicin on day 1 and methotrexate and 5-fluorouracil on day 8. Half of the 110 patients were randomly assigned to receive a synchronization program of 4 days of tamoxifen followed by 36 hr of Premarin on days 2 through 7 as well. This schedule had been demonstrated to induce optimal recruitment of hormone-dependent human breast cancer cells in tissue culture into the growth cycle. An overall summary of the trial results showed comparable response rates and survival in both patient groups. Partial responders treated with the synchronization program had a significantly longer response duration and survival. Unexpectedly 13 of 14 patients with inflammatory breast cancer showed a response to therapy, and the addition of hormonal synchronization to cytotoxic chemotherapy was significantly associated with achievement of a complete clinical response in that group of patients [9]. This led to an ongoing phase-II trial in which patients with locally advanced breast cancer (stages IIIA and IIIB) receive a similar chemohormonal regimen until a maximal clinical response is achieved. Definitive local therapy follows thereafter. Thus far the objective response rate is 94% in 58 consecutive evaluable patients and 54% have demonstrated a pathological complete remission after chemotherapy alone. About one quarter of patients have relapsed and median survival has not been reached [10].

The failure of the *in vitro* models of estrogen-mediated rescue of tamoxifen inhibition to translate reproducibly into positive effects *in vivo* may lie in the prolonged half-life of tamoxifen and its metabolites *in vivo*. Thus other studies have omitted tamoxifen, turning instead to the use of estrogen alone to recruit cells into the cell cycle. In a well-designed pilot study, Conte and colleagues evaluated the ability of diethylstilbestrol (DES) given daily for 3 days to stimulate tumor proliferative activity in 16 patients with locally advanced breast cancer who went on to receive standard 5-fluorouracil–doxorubicin–cyclophosphamide (FAC) chemotherapy on day 4. Tumor proliferative activity as measured by thymidine labeling index and primer dependent α-DNA polymerase labeling index was evaluated in tumor biopsies obtained immediately before and after DES treatment and 24 hr after chemotherapy. DES significantly

increased thymidine labeling rates in 8 of 16 patients while primer-dependent α-DNA polymerase labeling index was increased in 13 of 16 patients. Chemotherapy induced a rapid decrease in tumor proliferative indices. Interestingly, the observed increase in labeling indices was independent of estrogen receptor content of the tumor [11]. In a series of 39 patients with locally advanced breast cancer treated with DES–FAC prospectively these investigators observed a 72% objective response rate. These results led to a trial in 117 patients with metastatic breast cancer who were randomized to receive cyclophosphamide, epidoxorubicin, and 5-fluorouracil with or without the 3-day DES priming described above. Although projected drug doses were identical in the 2 arms, the study is marred by the fact that the drug schedules were quite different. All cytotoxic agents were given on day 1 in the control arm while cyclophosphamide was given on day 1 and epidoxorubicin and 5-fluorouracil were administered on day 8 after DES on days 5–7 in the synchronization arm. Response rate (50%), disease-free survival and overall survival were similar in the 2 patient groups. However, the flawed trial design makes it impossible to evaluate the role, if any, of estrogen recruitment [12]. In a slightly different study, the EORTC has also omitted tamoxifen, using instead chronic aminoglutethemide administration and cyclic chemotherapy with FAC preceded by a single dose of ethinyl estradiol. Preliminary results show an overall response rate of 75% in 57 patients with metastatic breast cancer and a randomized double-blind phase-III study is now in progress [13]. Clearly this type of approach warrants further study. However, in evaluating clinical results it will be crucial to monitor tumor kinetics where possible as Conte and coworkers have done so that we may know whether the stated goal of estrogen recruitment of tumor cells is in fact being achieved.

It is of note that similar approaches of hormone stimulation followed by exposure to chemotherapeutic agents have been used in treatment of metastatic prostate cancer. In a small patient series fluoxymesterone priming prior to treatment with methotrexate and cyclophosphamide resulted in a 43% response rate [14]. A randomized trial of continuous aminoglutethimide to lower adrenal androgen secretion with or without fluoxymesterone stimulation before chemotherapy with cyclophosphamide, doxorubicin, and 5-fluorouracil has been performed in 67 orchiectomized men with stage D2 prostate cancer. Although the response rate was higher in the stimulation than the control arm (85 vs. 72%), response duration and survival were virtually identical in the 2 groups. An increase in tumor cell activity due to androgens was implied by the increase in bone pain noted by patients during pulse androgen administration. In fact, 2 patients developed spinal cord compression on androgens [15]. A similar approach is under study in previously untreated patients with stage D prostate carcinoma at the National Cancer Institute. The anti-androgen, flutamide, and an LH–RH agonist, leuprolide, are administered chronically to effect a complete androgen blockade; patients then receive cyclical fluoxymesterone priming followed by high-dose carboplatin chemotherapy.

Traditional approaches to the treatment of breast cancer with chemotherapy or endocrine manipulation have failed to result in either cures or significant unmaintained complete remissions in women with metastatic disease. Combined chemoendocrine therapy may increase response rate or duration but has had only a modest impact on overall survival to date. Attempts to combine pulse hormone therapy with chemotherapy to increase tumor susceptibility to cytotoxic drugs have yielded similar results in metastatic breast and prostate cancers—probable enhanced response rate without marked improvement in survival. Thus there is probably no convincing indication for the routine use of chemohormonal synchronization approaches at present. However, studies in breast cancer have suggested that combined therapy administered in a priming schedule is certainly no more toxic than chemotherapy alone. Continued exploration of this approach with attention to timing of therapy and effects on tumor cell kinetics in the context of well-conceived trials continues to offer the promise of more effective therapies with existing agents.

REFERENCES

1. Lippman ME. Efforts to combine endocrine and chemotherapy in the management of breast cancer: do two and two equal three? *Breast Cancer Res Treat* 1983, **3**, 117–127.
2. Davidson NE, Lippman ME. Combined therapy in advanced breast cancer. *Eur J Cancer Clin Oncol* 1985, **21**, 1123–1126.
3. Weicheselbaum RR, Hellman S, Piro AJ, Nove JJ, Little JR. Proliferation kinetics of a human breast cancer cell line *in vitro* following treatment with 17β-estradiol and 1β-D-arabinofuranosylcytosine. *Cancer Res* 1978, **38**, 2339–2342.
4. Lippman M, Bolan G, Huff K. The effects of estrogens and antiestrogens on hormone-responsive breast cancer in long-term tissue culture. *Cancer Res* 1976, **36**, 4595–4601.
5. Kiss R, Paridaens R, Leclercq G, Danguy A. Sensitivity of the hormone dependent

MXT-mouse mammary carcinoma to estradiol during tumoral growth. An autoradiographic study. *Eur J Cancer Clin Oncol* 1986, **22**, 849–856.
6. Dao TL, Sinha DK, Nemoto T, Patel J. Effect of estrogen and progesterone on cellular replication of human breast tumors. *Cancer Res* 1982, **42**, 359–362.
7. Allegra JC, Woodcock TM, Steven D. A phase-II trial of tamoxifen, Premarin, methotrexate, and 5-fluorouracil in metastatic breast cancer. *Eur J Cancer Clin Oncol* 1986, **22**, 1786.
8. Bowman D. A phase-II evaluation of sequential tamoxifen, Premarin, methotrexate and 5-fluorouracil in refractory stage IV breast cancer. *Proc Amer Soc Clin Oncol* 1983, **19**, 415.
9. Lippman ME, Cassidy J, Wesley M, Young RC. A randomized attempt to increase the efficacy of cytotoxic chemotherapy in metastatic breast cancer by hormonal synchronization. *J Clin Oncol* 1984, **2**, 28–36.
10. Lippman ME, Swain S, Steis R, *et al.* Treatment of locally advanced breast cancer using primary induction chemotherapy with hormonal synchronization followed by radiation therapy with or without debulking surgery. *Eur J Cancer Clin Oncol* 1986, **22**, 729.
11. Conte PF, Fraschini G, Alama A, *et al.* Chemotherapy following estrogen-induced expansion of the growth fraction of human breast cancer. *Cancer Res* 1985, **45**, 5926–5930.
12. Conte PF, Pronzato P, Lionetto R, *et al.* Cytokinetic studies and treatment results of estrogen followed by chemotherapy in locally advanced (LABC) and metastatic (MBC) human breast cancer. *Eur J Cancer Clin Oncol* 1986, **22**, 728.
13. Paridaens R, Klijn JGM, Julien JP, Clarysse A, Rotmensz N, Sylvester R. Chemotherapy with estrogenic recruitment in breast cancer: experimental background and clinical studies conducted by the EORTC Breast Cancer Cooperative Group. *Eur J Cancer Clin Oncol* 1986, **22**, 728.
14. Suarez AJ, Lamm DL, Radwin HM, Sarosdy M, Clark G, Osborne CK. Androgen priming and cytotoxic chemotherapy in advanced prostate carcinoma. *Cancer Chemother Pharmacol* 1982, **8**, 261–265.
15. Manni A, Santen R, Boucher A, *et al.* Androgen priming and response to chemotherapy in advanced prostate cancer. *Proc Amer Soc Clin Oncol* 1986, **5**, 96.