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Perspectives and Commentaries

Combined Therapy in Advanced Breast Cancer

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(A COMMENT ON: Mouridsen HT, Rose C, Engelsman E, Sylvester R, Rotmensz N. Combined cytotoxic and endocrine therapy in postmenopausal patients with advanced breast cancer. A randomized study of CMF vs CMF + tamoxifen. *Eur J Cancer Clin Oncol* 1985, **21**, 291-299.)

BREAST cancer is a common malignancy in women in Europe and the United States. Less than 10% of patients are found to have overt metastatic disease initially; yet over one-third will develop and die of metastatic disease. Thus treatment of advanced disease has been the subject of intense investigation, and substantial progress has been made using both hormonal and chemotherapeutic approaches. However, recent results of treatment with combination chemotherapy have suggested a plateauing of success such that some 50-70% of patients may be expected to respond to current first-line drug combinations, with a median response duration of 6-12 months and a median survival of 12-24 months. Similarly, the response rate to endocrine manipulation, whether ablative or medical, is no more than 35% in an unselected patient population and median response duration rarely exceeds 1 yr. The development of estrogen and progesterone receptor assays has improved our ability to select patients likely to benefit from an endocrine intervention but obviously in no way affects the overall results for a given therapy.

This therapeutic impasse has led to the investigation of a number of approaches to improve results of treatment, amongst them the use of combined chemoendocrine therapy. Such a trial using cyclophosphamide, methotrexate and 5-fluorouracil with or without tamoxifen has been reported by Mouridsen *et al.* [1].

The theoretical rationale for a combined approach is clear. Breast cancer is a heterogeneous disease. These two treatment modalities appear to exert their antineoplastic effects by separate mechanisms of action. Therefore combination therapy may have an additive or even synergistic effect in disease treatment. Furthermore their differing toxicities may make it possible to administer simultaneously two therapies of proven efficacy in an intensive fashion with manageable side-effects.

Unfortunately a number of potential objections can also be identified [2]. Foremost is the observation that an additive effect may be less rewarding than anticipated. Given the response rates to the individual therapies already cited, an improvement in response rate of 10-20% at best can be expected with combined therapy. Second, in the advanced disease setting where attainment of a complete response can in no way be equated with cure, there is no indication that combined therapy will be more effective than sequential therapy. Indeed, there are several possible disadvantages of the combined approach. It is impossible to identify which therapy is beneficial, making it difficult to delete ineffective and possibly toxic drugs, and hampering one's ability to choose a subsequent therapy, for example, a second-line endocrine therapy on the basis of the success of the first. Third, a number of possible detrimental interactions between endocrine and chemotherapeutic approaches may be imagined. Change in hormone milieu may affect hepatic enzymes and drug metabolism or alter immune status. Tamoxifen may cause a mild myelosuppression leading to a dose reduction of concomitant chemotherapy. Finally, endocrine intervention may perturb cell cycle kinetics so as

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torender the cell less responsive to chemotherapeutic agents. It has been shown *in vitro* that treatment of breast cancer cells with antiestrogens induces a reversible G_1 arrest. Chemotherapeutic agents are frequently most active against rapidly dividing cells. Thus a cytostatic endocrine therapy which leads to a small fraction of cycling cells may in fact protect the tumor from the effects of chemotherapy and decrease the overall response rate to the combined therapy as compared to sequential use of the same therapies.

Nonetheless a number of clinical trials involving combined hormono- and chemotherapy have been undertaken. Frequently they have failed to address the crucial question regarding combined therapies — whether or not total response and survival of patients treated with combined therapy is superior to that which may be obtained by sequential administration of the same treatments. Trials of this type require longer periods of follow-up than single modality studies, often necessitate a cross-over design and may require large numbers of patients in order to observe a difference in response rate of the magnitude previously predicted.

Several early trials examined the addition of chemotherapy to oophorectomy in premenopausal women; most compared a simultaneous treatment arm with the sequential administration of chemotherapy after failure of oophorectomy [3, 4]. Overall they suggest that superior response rates and duration can be achieved with the combined approach but no compelling evidence for improved overall survival has emerged. Studies with the addition of androgens, progestins or diethylstilbestrol to combination chemotherapy have been equally unrewarding [3, 4]. Most recent trials have focused on the addition of an antiestrogen, tamoxifen, to standard chemotherapeutic regimens in either a concurrent or sequential schedule [3, 4]. The overall response rate and time to progression are generally enhanced but improvement in survival has not been convincingly demonstrated. It is noteworthy that the same conclusions may be drawn from similar studies of chemoendocrine therapy in the adjuvant treatment of breast cancer [5]. An increase in disease-free survival with the combined approach is often noted but overall survival remains essentially unchanged, suggesting simply a postponement of clinically apparent disease recurrence. In at least one case, however, survival in a subset of premenopausal women with estrogen receptor-negative tumors who were treated with L-phenylalanine mustard, 5-fluorouracil and tamoxifen was shortened compared with survival of their peers who did not receive tamoxifen [6]. This raises the possibility that some of the potential negative interactions previously mentioned may have contributed to the adverse results. Indeed, recent combined data from the adjuvant literature suggest the possibility of a negative interaction between endocrine therapy and chemotherapy as well [7].

The study of Mouridsen *et al.* [1] also demonstrates a significant increase in response rate with combined modality treatment but median duration of remission and survival are only slighly improved. It is unfortunate that no information regarding the incidence of subsequent tamoxifen therapy in CMF failures is available to evaluate the efficacy of combined vs sequential therapy, nor are receptor data presented to aid our analysis. Even though the trial was properly randomized, a modest imbalance in prognostic factors, including prior therapy and performance status, favoring the combined therapy arm is noted. This slight difference in patient populations could account in part for the more favorable outcome in the CMF-tamoxifen group.

A different approach to combined therapy has been to use endocrine therapy to induce a synchronously stimulated wave of tumor cell proliferation followed by chemotherapy. Support for this approach may be drawn from cell culture data, suggesting that estrogen deprivation induced by tamoxifen followed by physiological estrogen replacement induces a marked increase in breast cancer cell growth fraction [8]. In addition, an increased thymidine labeling index in the tumor cells of patients with skin or subcutaneous metastases who have been exposed briefly to physiologic doses of estrogen and progesterone has been observed [9]. A trial of this type using cyclophosphamide and doxorubicin on day 1 and methotrexate and 5-fluorouracil on day 8 was recently completed at the National Cancer Institute in Bethesda [10]. Half of the patients were randomized to a synchronization program of 4 days of tamoxifen followed by 36 hr of premarin, a schedule which had been shown to induce optimal rescue of hormone-dependent human breast cancer cells in tissue culture. A significant improvement in time to progression and survival was seen only in the subset of patients who demonstrated a partial response to the combined therapy, although in an uncontrolled trial 43 patients with locally advanced disease undergoing the synchronized treatment demonstrated a 90% response rate, with 56% of patients attaining a complete remission. A similar phase II trial of tamoxifen-premarin synchronization followed by methotrexate and 5-fluorouracil initially showed a high response rate of 75%, with complete responses in 56% of patients

[11]. Unfortunately these results were not duplicated in a second trial using an identical regimen but in more heavily pretreated patients [12]. The failure of this *in vitro* model 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*. Another phase II study using chronic aminoglutethimide administration and cyclic chemotherapy with 5-fluorouracil, doxorubicin and cyclophosphamide (FAC) preceded by a single dose of ethinyl estradiol also demonstrated a 74% response rate [13]. Of note, a similar technique of hormone stimulation followed by exposure to chemotherapeutic agents has been used in metastatic prostate cancer, both in a rat model and in man. In man fluoxymesterone-priming prior to treatment with methotrexate and cyclophosphamide resulted in a 43% response rate in a small patient series [14]. A randomized trial of continuous aminoglutethimide with or without fluoxymesterone priming before FAC therapy is ongoing, with preliminary results showing an increased response rate in the androgen-primed patients [15]. An increase in tumor cell activity upon exposure to androgens was implied by the increase in bone pain noted in both studies during the period of androgen administration. All of these findings suggest that combined therapy administered in this manner is certainly no more toxic than the chemotherapy alone. Further exploration of timing of therapy and effects on tumor cell kinetics *in vivo* is warranted.

Traditional approaches to the treatment of metastatic breast cancer with chemotherapy or endocrine maneuvers have failed to result in a cure or even a significant unmaintained disease-free survival in women with advanced disease. Combined chemoendocrine therapy may increase response rate and duration but has had only a modest impact on overall survival to date. Thus there is probably no convincing indication for the routine use of chemohormonal treatment at present. Nonetheless, continuing investigation using new approaches in the context of well-conceived randomized trials is clearly warranted.

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