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RATIONALE FOR COMBINING CHEMOTHERAPY AND HORMONAL THERAPY IN BREAST CANCER

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Summary—Both chemotherapeutic agents and hormones are effective in breast cancer treatment. Their mechanism of action seems to be conflicting: while cytotoxic drugs are active on cycling cells, hormones prolong the G_0 phase. Therefore, the concurrent use of hormones and chemotherapy could decrease their expected clinical activity. On the contrary, a review of the literature suggests that there could be some synergistic action with combined therapy. The problem is therefore to assess the efficacy of simultaneous vs sequential administration of hormones and chemotherapy. In advanced disease the general conclusion could be that simultaneous administration of combined therapy: (1) increases, although the difference is not statistically significant, the response rate both in pre and postmenopausal patients; and (2) the most important end point, total survival, is not statistically improved by simultaneous vs sequential administration. In addition, in the adjuvant setting combined treatment appears superior to chemotherapy only in postmenopausal, receptor-positive patients. No definite conclusion is today available in premenopause.

INTRODUCTION

Following the first successful attempts by Greenspan[1], a real breakthrough in advanced breast cancer treatment has been a multidrug combination regimen adopted by Cooper in 1969 [2]. Today, after a decade of trials, results indicate that 5, 4 and 3 drug regimens (CMFVP, CMFV, CMF) [3–7] and more recently adriamycin-including regimens do not possess significant differences in efficacy [3, 7–9]. Approximately 60% of the patients treated with any of these drug combinations will show tumor regression, but less than 20% will achieve complete remission. Median duration of response is not more than 10 months and median duration of survival from initiation of treatment is 2 years. After much debate it is now accepted that response to chemotherapy is unrelated to hormone receptor status [10].

Endocrine therapy has been the mainstay of advanced breast cancer treatment since oophorectomy was first used in premenopausal women by Beatson 75 years ago. In unselected patients a response rate of approx. 30% can be obtained with ablative therapy (oophorectomy) in premenopausal women and with additive treatments (estrogens, androgens, progestogens and more recently antiestrogen and aminoglutethimide) in postmenopausal patients. Median duration of response after endocrine therapy is not in excess of 10–12 months [11, 12].

Considering only receptor-positive patients the expected response rate increases to approx. 60%. At the present time, after various clinical trials, accepted standard endocrine treatment is considered to be oophorectomy and/or antiestrogen in premenopause and antiestrogens (tamoxifen) in postmenopause. Tamoxifen is chosen not for greater efficacy but because it is practically devoid of side effects [11].

In spite of the fact that endocrine therapy has been clinically applied for many years, its mode of action remains somewhat unclear.

At low doses estrogens induce sensitive cells to proliferate, increasing the growth fraction through the synchronous recruitment of G_0 cells and a reduction of the generation time of cycling cells mainly in the G_1 and S phases. These effects are reversed by hormone deprivation. Therefore oophorectomy and/or antiestrogen activity in premenopause is explained by the sudden removal of the main endogeneous source [13, 14]. The striking responsiveness of cultured cells to extremely low concentrations (5×10^{-10} M) of estrogens in the medium implies that, in the clinical setting, peripheral conversion of adrenal androgen precursors to estrogen may occur at such a rate as to counterbalance removal of the ovarian source. This mechanism could in part explain why 30% of receptor positive patients do not respond to ablative therapy.

Additive therapy on the contrary is more difficult to interpret. The dose–response curve of estrogens is biphasic: small doses induce cell proliferation, whereas higher doses decrease cell proliferation, eventually resulting in cell death. The only evidence suggesting that this effect is receptor mediated comes from clinical data since two-thirds of receptor-positive patients are responsive to hormone treatment vs 10% of receptor-negative patients, while in cell cultures this effect seems to be nonspecific [13]. We can assume that only a low percentage of receptor-negative patients respond mainly because of both cell heterogeneity and the nonspecific toxic effects of high dose additive endocrine treatment.

Since antiestrogens inhibit cell proliferation and decrease thymidine incorporation into DNA only in receptor-positive cells lines, they are thought to reduce reproduction rate by blocking the cells in G_0

quiescent state through an estogen-mediated mechanism. Tamoxifen effects are reversed by simultaneous or sequential administration of 10-fold lower concentrations of estradiol if exposition to tamoxifen is not prolonged for more than 48 h. The rate of thymidine incorporation after estradiol rescue is significantly greater than after treatment with estradiol alone, in keeping with the hypothesis that a single cohort of cells is shifted into the cycle after removal of the tamoxifen block. In long-term cultures a small ($10^{-5/6}$) number of morphologically indistinguishable resistant cell clones emerge [13, 14]. Transferring these data to the clinical setting, the short-lived period of clinical response in receptor-positive patients could be the consequence of tamoxifen-induced reduction of only the receptor-positive cell reproduction rate through a G_0 block with a cytocydal effect occurring only in a few lines. Resistant clones could emerge and receptor-negative lines already present in the cancer tissue could increase unchecked.

The above data lead to two divergent hypotheses:

(1) Both hormonal and cytotoxic therapies have reached their efficiency plateau; both types of therapies are effective, but side effects and mechanism of actions vary [15]. Breast tumors are made up of variable mixtures of receptor-positive and receptor-negative clones, the prevalence of which determines the receptor status of the single tumor. In receptor-positive tumors, a simultaneous combination of both hormonal and cytotoxic treatments should increase the overall regression rate, number of complete remissions, mean duration of remission and mean duration of survival following treatment.

(2) If the mechanism of action of the two therapies differ, each acts on and induces different kinetic states in the cell population, with results that theoretically can be conflicting [16]. Cytotoxic drugs kill proliferating cells; the reduction in cycling cells spurs more and more G_0 quiescent cells to enter the cycle and the net result is an increase in the growth fraction. In an advanced tumor in the kinetic "plateau" phase the end result is determined by the small portion of actively cycling cells present at the beginning of treatment [17]. On the contrary, endocrine treatment induces a prompt fall in the labeling index of responding tissues since the cells are blocked in the G_0 state. Therefore the reduction in reproduction rate seems to be a more important mechanism of action (of ablative and antiestrogen therapy) than the actual cell kill but even after additive estrogen therapy nonspecific cytocydal activity could be unrelated to cell cycle and phase. It is therefore conceivable that the ensuing reduction in growth produced by endocrine manipulation hinders the effect of simultaneous chemotherapy resulting in a decreased tumor cell kill compared to that obtained with chemotherapy alone. This theory has been substantiated by experimental results. Small physiologic doses of 17β-estradiol, which induce a higher LI, and aracytin had a synergistic action while higher, therapeutic doses, of 17β-estradiol, which decrease the growth rate, reduced cytotoxic drug activity [18].

A critical analysis of trials with chemohormone therapy in breast cancer follows.

ADVANCED DISEASE

Premenopausal studies

In premenopausal women oophorectomy has been combined with various polychemotherapy regimens given either concurrently or at tumor progression. The results of various trials are fairly comparable [19–23]. In 1977 Ahman *et al.*[19] reported the first randomized trial of simultaneous vs sequential treatment (oophorectomy/chemotherapy). Objective response was greater, although the difference was not statistically significant, in the group receiving concurrent chemotherapy compared to the group treated with oophorectomy alone. When subsequent responses to chemotherapy, instituted following progression after ooophorectomy, were taken into account no difference in overall response was detectable between the two modalities of combined treatment. In terms of progression free interval concurrent endocrine and cytotoxic therapy is clearly advantageous. However, there is no difference in overall survival between treatment groups [19].

In a CALGB study, where oophorectomy was followed by: (1) observation, (2) monochemotherapy and (3) polychemotherapy (VPCMF), the response rates (complete + partial) were 18, 65 and 72% respectively, showing that, while concurrent polychemotherapy is not superior to monochemotherapy, a significant difference exists between oophorectomy alone and concurrent treatment. However, since patients progressing after oophorectomy experienced a 50% response rate to subequent chemotherapy, no real gain in response can be ascribed to any of the three arms. No doubt the rate at which patients enter response and the median duration of response (17 and 16 vs 5 months, respectively) are superior for the groups initially receiving chemotherapy but the overall survival is superimposable [22].

A slightly different trial has been recently reported by the Swiss Group for Clinical Cancer Research [21]. In this trial patients were randomized to concurrent oophorectomy and chemotherapy and to oophorectomy followed in 6–8 weeks by chemotherapy, except in cases of confirmed tumor regression when chemotherapy was postponed. No difference in response rates was detectable between concurrent and sequential treatment even if the

median time to progression in responders was significantly shorter after oophorectomy alone than after concurrent treatment. As in the CALGB study, response to oophorectomy did not negatively influence subsequent response to chemotherapy. Again no significant difference in survival was evident between concurrent and sequential treatments. As expected, the only significant difference in survival was determined by response [21].

Postmenopausal studies

Postmenopausal studies evaluating the effectiveness of combined chemohormone therapy are more numerous. More variables are to be considered: the kind of additive endocrine treatment employed and the design of the study: (1) chemohormone treatment vs hormone treatment; and (2) chemohormone treatment vs chemotherapy [12, 15, 20, 21, 24–32]. In the end most studies turn out to be comparative trials between concurrent and sequential combined treatments since, unless receptor negative status can be assessed, withholding a potentially beneficial therapy could be considered unethical.

In a few studies an androgen additive treatment was tested. The overall response reported in the Arizona study with calusterone and a polychemotherapy regimen was greater but not significantly so in the combined arm, the median duration of remission was significantly longer compared to the arm with chemotherapy only. The overall survival was also significantly superior in the combined arm ($P < 0.05$). There was an even more evident difference in survival between responding patients in the two arms ($P < 0.01$). Since at disease progression protocol treatment was discontinued and patients received further polychemotherapy, this study suggests that simultaneous therapy is more effective. However the authors draw their conclusions from data based on a limited period of the clinical course without considering previous and subsequent treatments.

In another report evaluating polychemotherapy with and without concurrent administration of norethisterone acetate, heavy endocrine pretreatment of the enrolled patients does not permit a correct evaluation of any treatment advantages [30].

A carefully planned randomized trial was started in 1976 by Kiang *et al.*[27]. None of the patients had been previously exposed to endocrine or chemotherapy and if accessible tissue was available they were stratified according to estrogen receptor (ER) concentration. The endocrine agent was diethylstilbestrol (DES). In the ER+ and ER undetermined groups concurrent treatment (DES+ CTX + 5FU) was tested against a sequential treatment in which patients failing to respond or relapsing after DES were treated with CTX + 5FU. In the ER− group patients were randomized to the above chemohormone combination treatment vs chemotherapy alone.

In the ER+ patients the response rate (complete + partial) was higher, though not significantly so, after concurrent treatment (87 vs 64%). Analysis of overall results of sequential treatment (responses to either DES or CTX + FU) shows that the response rate climbed to 80%, becoming superimposable to the concurrent arm. Median duration of response was also similar in the two groups. However, overall survival appears longer with concurrent therapy even if the number of patients at risk, 22, is too low to rule out a type B error.

For ER undetermined groups survival data initially favored the concurrent treatment arm but no difference is now evident. ER− patients also had improved response with combined treatment but globally they fared poorly. We are of the opinion that these results do not show any clear advantage of concurrent vs sequential use of combined treatment [15, 27]. A recent South African report of similar design with tamoxifen instead of DES clearly demonstrates no advantage with concurrent treatment. Sequential tamoxifen–CMF treatment yields the same overall percentage of response, median duration of response and median survival, as concurrent CMF + tamoxifen. A very important prognostic factor in predicting survival is the ER level [24].

The Swiss Group for Clinical Cancer Research has recently reported its final results concerning sequential vs simultaneous treatment in postmenopausal patients where hormone treatment was represented by tamoxifen and patients were randomly allocated to start cytotoxic therapy immediately or to delay chemotherapy for 6–8 weeks, except in cases of confirmed tumor regression. Comparing the South African and the Swiss studies a slight difference in design is apparent. In the first investigation, in the sequential arm, progression or failure provided the indication to start chemotherapy, while in the second study chemotherapy was always added to tamoxifen, except in cases of definite tumor regression. As in the South African study the overall response rate was similar in both groups (61 vs 61%). In both studies hormone pretreatment did not influence subsequent response to cytotoxic treatment (42 and 52%). No difference in survival was evident between the two groups [21].

In a recent Italian study patients were given chemotherapy (CMF) with or without tamoxifen at random. The patients failing combined treatment underwent successive regimens; patients failing CMF alone were treated with combined CMF–tamoxifen treatment to evaluate tamoxifen activity while continuing suppression of chemosensitive clones with CMF. If tissue was available, ER was determined. Both treatment groups were statistically comparable and similar numbers of patients in the two groups had previously undergone endocrine treatment. A statistically significant difference ($P < 0.01$) in response rate (74 vs 51%) in favor of the concurrent treatment (mainly when measurable dominant lesions

were osseous) was observed in both untreated and hormonally pretreated patients. As expected, the difference in response was highly significant in ER+ patients. Median duration of objective remission was similar in both groups but since a 31% remission rate was achieved by CMF–tamoxifen after failure or progression on CMF alone, overall rates of response were similar, at the end, in the two arms. Overall survival was longer for patients on CMF than for patients on CMF–tamoxifen, however the difference was not statistically significant. As expected, survival curves were significantly superior for responding patients in both groups [26]. In conclusion these data seem to indicate that neither chemo nor hormone first-line treatment influences further response to the alternative treatment.

Results from a similar study carried out at our institute support the same general conclusions, suggesting improved response rate and time to progression, but no statistical difference in survival with combined treatment vs chemotherapy only [25]. Medroxiprogesterone acetate when substituted for tamoxifen gives very similar results [29].

Even though, contrary to the above, a recent EORTC study demonstrates a significantly superior survival (not only an increased response rate) with concurrent treatment, this study along with that of the Arizona group does not take prior treatment into account [32].

Most of the studies reported here have not used steroid receptor data to select patients. Knowledge of receptor status could have spared some premenopausal patients an unnecessary surgical procedure and some postmenopausal patients unnecessary side effects but unfortunately, even now, most patients fall into the receptor-unknown group for lack of accessible tissue in the case of osseous and/or visceral metastasis.

Except for receptor-negative patients, combined treatment can be suggested in most cases and usually the sequential use of the two modalities is advisable in common clinical use. By using this sequence, subsequent responses could be achieved, sparing the patients concomitant side effects and improving the quality of life which, in an incurable disease, becomes the principal aim.

One British study addresses the question of whether the success or failure of one form of primary treatment jeopardizes chances of subsequent response to an alternative treatment. The reported results rule out any survival advantages whether chemotherapy or endocrine therapy were adminstered initially. Again the rates of response and median duration of response were lower with endocrine treatment only but the end result, survival, is not affected [33].

One of the aims of sequential treatment, besides providing a better quality of life, could be increased survival. This result could have been masked in most studies due to the fact that patients had already undergone previous treatments and after failure or progression did not receive homogeneous second- and third-line salvage therapies.

A well-designed study showed that improved survival can be attained with optimal sequential therapy, meant to avoid any premature exhaustion of therapeutic modalities [34]. According to the study outline receptor-positive and previously untreated patients with ER undetermined, underwent primary hormonal treatment and, if they responded to the initial therapy a second hormone therapy was administered. At relapse patients underwent the same treatment reserved for previously untreated receptor-negative patients, following an orderly sequence of first-line (2–3 drug chemotherapy CF/CFP), second-line (CMFVP) and third-line (adriamycin-including regimen) chemotherapy. This chemotherapy sequence had already proved effective in producing additional response [35]. The median survival for patients responding to both endocrine and chemotherapeutic sequential treatment was significantly prolonged compared to that of patients responding either to hormone or chemotherapy ($P < 0.001$). As in the previously mentioned British study, no detrimental effect in the chemotherapy response could be attributed to the first-line hormone treatment. Also, in this study receptor status predicted the biological aggressiveness of the tumor, so that even if they responded to chemotherapy, median survival of receptor-negative tumors was 31 months, not significantly less than ER+/ER undetermined patients responding only to chemotherapy, but significantly inferior to responding ER+ patients who benefited from two sequential regressions. Non-responding patients, as expected, fared decidedly worse.

To utilize the divergent effects of estrogens and antiestrogens, in two studies, metastatic patients have been treated sequentially with: (1) tamoxifen to arrest a fraction of cells in a uniform phase of the cell cycle; (2) a subsequent boost of estradiol to induce a larger synchronized cohort of cells through the S phase; and (3) cycle-specific cytotoxic chemotherapy. The recently published results of the first study (69% overall remission, 47% complete remission) are undoubtedly impressive and seem to prove the underlying rationale [36]. These are the results of a pilot study, where conclusions could be biased by the highly selected patient group. The results of the second randomized study, whose update is to be presented at this meeting, deny that there is an advantage in using this kinetically designed treatment. We must therefore conclude that at the present time new ways to exploit the different kinetic mechanisms of hormones and drugs have to be undertaken and evaluated.

ADJUVANT STUDIES

Here the kinetic situation is very favorable since we presume that the residual subclinical tumor mass, after primary tumor removal, is in the order of

$10^6/10^9$ cells and, consequently, the growth fraction is fairly high [17]. In addition, the expected number of naturally occurring mutant resistant cells is fairly low [37].

Adjuvant studies employing oophorectomy in premenopausal women do not offer convincing evidence of significantly prolonged survival, even if most attain significant disease-free survival (DFS), but they are biased by the lack of stratification according to the now well-recognized prognostic parameters of nodal status and ER determination.

No definitive results from ongoing clinical trials of additive hormonal treatment are available although the positive results of adjuvant chemotherapy are well known.

Many studies have therefore been started to verify whether the higher rates of responses achieved with simultaneous combined treatment in advanced disease could be translated into an increased cure rate when used in the adjuvant setting where, theoretically, more favorable conditions could allow a greater and definite reduction of the residual micrometastasis, without inducing selective outgrowth and/or emergence of resistant clones. A Western group case study shows a definite advantage in DFS adding tamoxifen to CMF in ER+ premenopausal and postmenopausal axillary node positive (N+) patients. The premenopausal data are unfortunately biased by the use of a lower than conventional dosage of CMF, if we accept the hypothesis that full dosages of drugs are essential to achieve significant results in prophylactic therapy [38].

A recent 3-year update of the NSABP study holds that, while the advantage in DFS and survival (S) is present in receptor-positive postmenopausal patients treated with polychemotherapy (PF) and tamoxifen, no significant difference is evident in premenopausal patients [39]. As in a previous report, the magnitude of the effects is directly linked to the level of receptor positivity. The benefit is evident in both axillary node categories 1–3, $\geqslant 4$, even if to a greater extent in the latter. A detailed analysis of the study shows a strict correlation, in predicting the advantage of tamoxifen therapy, in ER+ and to a greater extent PR+ patients. In fact, if PR levels are less than 10 fmol, no benefit in DFS and S is observed upon addition of tamoxifen regardless of the ER level. Undoubtedly the effect of tamoxifen is greater in those patients with tumors having both ER and PR levels higher than 10 fmol. While no advantage is evident in the receptor-negative postmenopausal patients and receptor-positive premenopausal patients, a significantly lower DFS and S is apparent for receptor-negative premenopausal patients. These adverse effects are difficult to explain in view of the fact that receptor-negative cells should be only unresponsive to the tamoxifen effect. The authors suggest an activation of receptor-targeted liver cells, speeding up drug metabolism and reducing chemotherapy effectiveness.

The doubts cast by these results on the use of tamoxifen as adjuvant therapy in premenopausal women prompted ECOG to run two randomized adjuvant studies of chemotherapy plus tamoxifen in pre and postmenopausal patients, to decode the premenopausal study [40]. The interim report at 4 years (median follow-up at 28 months) shows no statistical difference in DFS and S among chemotherapy (CMF or CMFP) and chemotherapy + tamoxifen (CMFPT), regardless of the nodal and receptor status. This study contradicts the detrimental effects reported by the NSABP in ER-patients, but emphasizes that a clear advantage can be expected only in postmenopausal patients.

CONCLUSIONS

From the above review of randomized trials it appears that simultaneous administration of combined therapy: (1) increases the response rate both in pre and postmenopausal patients, but the difference is not statistically significant; (2) the response rate has always been consistently lower in the endocrine treatment arm only; (3) the most important end point, total survival, is not statistically improved in any study, in spite of advantages in initial response, duration of response, time to progression and DSF.

This does not exclude the possibility that there are subgroups of patients that could benefit from a simultaneous combination. For instance, in both pre and postmenopausal patients, simultaneous combined treatment should be selected to control extensive and rapidly growing tumors: if the first treatment fails, the patient could be too ill to receive a second. Reconsidering our two initial hypotheses it seems that hormone manipulation and chemotherapy are apparently not in negative competition as some experimental data could suggest. Drugs and hormones may act on different tumor cells on a random basis, hence their action is additive in terms of response, even if not synergistic. But the short-lived duration of response, even if superior to that achieved with either therapy alone, shows the inability of the combination to wipe out all but the tip of the tumor iceberg. When tumor resistant clones grow, available weapons are already exhausted and are unable to counteract tumor progression. Even though adjuvant studies are still in progress, they seem to suggest that combined treatment is beneficial, but considering the natural history of the disease, their interpretation is premature.

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