Tamoxifen and Aminoglutethimide in Advanced Breast Cancer¹

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Abstract

Tamoxifen (TAM), a standard endocrine treatment for advanced breast cancer, probably acts by competing for the estrogen receptor protein in the breast tumor cells. If so, resistance to TAM may be a function of the level of the available endogenous estrogen. Inhibition of estrogen synthesis by aminoglutethimide may therefore facilitate the action of the antiestrogen. To test this hypothesis, the two agents were given concurrently (a) to patients who had become resistant to TAM and (b) to patients who had never received TAM in a randomized cross-over study against TAM alone. Patients with estrogen receptor protein-negative disease were excluded. Estrogen and aminoglutethimide levels were measured serially.

In the first study, four of 26 patients experienced partial responses, and four of 26, stabilization of their disease. In the randomized study, four of 11 patients on the combination and three of nine on TAM alone had responses. Two patients on the combination and three on TAM alone had stabilization of disease. In the first group, the low rate of response may be attributed to extensive prior treatment. In the randomized study, there is presently no clear advantage for one treatment, and overall, there was no statistically significant correlation between degree of estrogen suppression, aminoglutethimide level, and response.

The findings do not exclude the possibility that these agents may act in breast cancer by mechanisms other than inhibition of estrogen receptor.

Introduction

Endocrine therapy can induce objective remissions in about 30% of patients with breast cancer (6). An ERP³ may be identified in the cytoplasm of breast cancer cells in approximately 60% of patients. Endocrine therapy may produce response rates as high as 55% in these ERP-positive patients (5). Among the endocrine therapies, tamoxifen has been widely adopted as standard treatment (5). As an antiestrogen, it is as effective as other hormone manipulations, including surgical castration, in the induction of tumor regression; its advantages are ease of administration and relatively little toxicity.

The drug probably competes with estrogen for ERP in the tumor cells (11, 12, 23), although there is also evidence for a noncompetitive action (3). The drug has caused lysis of breast cancer cells growing in vitro in an estrogen-free medium, although addition of estrogen partly or completely reversed this effect (13). The importance of estrogens for the survival and growth of breast cancer cells is evident from clinical and laboratory studies (15). In some patients, hypophysectomy reduced endogenous estrogens and resulted in tumor cell lysis (9). In animal studies, 7,12-dimethylbenz(a)anthracene-induced enlarging mammary tumors in rats can be shown to undergo autolysis by estrogen ablation (8). Similarly, in human MCF-7 cell lines in vitro, synthesis of DNA is estrogen dependent (13).

While much of the laboratory evidence points to tamoxifen acting as a competitive inhibitor of ERP, clinical experience indicates that laboratory studies provide inadequate models for response and resistance. Some patients with strongly ERP-positive tumors may be resistant to antiestrogen, and others respond to estrogen ablation and to estrogen therapy regardless of the sequence of treatment (6).

These observations and the general experience that eventual hormone resistance is inevitable point to the urgency for a better understanding of drug resistance so that appropriate modification in endocrine therapy can be offered. One possible mechanism of resistance implied from studies of human prostatic carcinoma is that subpopulations of cells, which were initially resistant to hormones, emerge from a heterogenous tumor population (7). However, it is reasonable to postulate that a reduction in the level of available estrogen might facilitate the action of tamoxifen and thus improve the clinical response rate and prolong the duration of that response.

Aminoglutethimide reduces available estrogens by inhibiting estrogen synthesis in 2 ways (19). It inhibits the synthesis of adrenal and extraadrenal C₁₈ steroids which are estrogen precursors and also inhibits the peripheral conversion of androgen to estrogen (1, 18–20). In both pre- and postmenopausal women, aminoglutethimide decreases estrone, estradiol, urinary-free cortisol, androstenedione, aldosterone, and dehydroepiandrosterone levels (18). Therefore, it may be reasonable to anticipate that the lowering of estrogens by aminoglutethimide may enhance the effectiveness of the antiestrogen tamoxifen.

To test this hypothesis, we have treated 2 groups of patients, women who had been treated previously with tamoxifen and women who have never received tamoxifen. In addition, total estrogen levels have been measured serially in these patients in an effort to further elucidate the relationship between a fall in estrogen level and a clinical response to therapy.

Materials and Methods

Two studies are reported here. In the first, only patients who had been treated previously with tamoxifen and were known to have failed that therapy or were known to have responded and subsequently relapsed were treated with a combination of tamoxifen and aminoglutethimide. This was an uncontrolled study and served as a pilot for a more definitive, randomized trial. In the latter, only patients who were untreated previously with endocrine therapy were eligible for randomization to receive either tamoxifen alone or in combination with aminoglutethimide.
The doses of drug administered in the 2 studies were the same. Tamoxifen, 10 mg, was given twice daily either alone or in combination with aminoglutethimide. Aminoglutethimide, 250 mg, was administered daily during the first month to lessen the side effects commonly seen on initial treatment; thereafter, it was given 4 times daily until the patient went off therapy. All patients treated with aminoglutethimide were routinely given hydrocortisone, 20 mg, twice daily for the duration of the aminoglutethimide treatment. This dose was increased occasionally at the discretion of the primary physician to 40 mg twice daily during the first 2 to 4 weeks if the patient experienced a rash or other untoward effects.

Only patients who had histologically confirmed metastatic breast cancer and measurable sites of disease were eligible for either of the protocols. Patients completing a course of tamoxifen immediately prior to entry into the nonrandomized trial were maintained on tamoxifen without a break in therapy. A patient was accepted for the program only if the primary physician and the protocol chairman considered her life expectancy to be greater than 3 months. If ERP status was known, only patients with ERP-positive tumors were eligible. However, patients whose ERP was unknown were also accepted if (a) the DFI was long (usually in excess of 2 years); (b) nonvisceral disease predominated; and/or (c) the patient was more than 5 years postmenopausal. Patients who had received any prior hormone therapy were ineligible for the randomized trial, but this did not exclude patients from the nonrandomized study.

The criteria by which responses were scored are similar to those defined by the International Union against Cancer (4). Types of disease considered unmeasurable included pleural effusions, ascites, central nervous system lesions which had been irradiated, and those with elevated blood levels of carcinoembryonic antigen and liver enzymes.

Serum and plasma were obtained for pharmacology studies before administration of drug on the morning therapy was initiated and at the beginning of the second, fourth, sixth, eighth, and 12th weeks of the protocol. Bloods were drawn between 6 a.m. and noon but before the patient had taken her morning dose of tamoxifen or aminoglutethimide-hydrocortisone. Total estrogens were measured by radioimmunoassay utilizing antisera purchased from Radioassay Systems. Total estrogens were extracted from 2 ml of plasma with chloroform and concentrated, and the equivalent of 1/2 ml of plasma was assayed in duplicate. Appropriate recovery and known concentration controls were included in each assay. All plasmas from each patient were assayed simultaneously to avoid any interassay variation. Aminoglutethimide was measured by the color reaction described by Douglas and Nicholls (2), modified for appropriate amounts of plasma and by initial extraction of the aminoglutethimide and its metabolite with chloroform.

Time to treatment failure was plotted by the Kaplan-Meier method. The Fisher exact test was used to test differences in percentages. Estrogen levels were compared using the Wilcoxon test.

Results

Nonrandomized Study. A total of 35 patients has been treated in the nonrandomized study. Of these, 3 failed to fulfill the eligibility criteria described above: 2 because their disease was not measurable and one because her prior response to tamoxifen was invaluable. In addition, 6 patients were invaluable because therapy was discontinued before evaluation was possible. Four of these patients discontinued tamoxifen-aminoglutethimide within the first month due to toxicity; 2 others had slightly more than 1 month of therapy, but their dose of aminoglutethimide never exceeded 500 mg/day. Of the 26 patients who were both eligible and evaluable, one-half were treated for only 3 months because their disease had progressed within that time.

The patients in the nonrandomized trial were heavily pre-treated. All had received prior tamoxifen, but only 10 (35%) had experienced a prior response to tamoxifen. Eleven of the patients had been given other prior endocrine therapy previously, but only 4 of these had responded to that therapy. Two patients had responded to both tamoxifen and a second form of endocrine therapy before beginning the combination tamoxifen-aminoglutethimide. In addition, 17 (65%) of these patients had also received prior chemotherapy, and 6 had been treated with 2 or more chemotherapy regimens. In one-half of the patients, metastatic disease had been present for at least 2 years, one-fourth had had metastases for more than 4 years, and 3 patients, for more than 5 years. Nineteen (73%) had disease involvement at 3 or more sites.

By conventional criteria, the patients were typical candidates for endocrine therapy. The median age was 57 years (range, 37 to 69), and the median DFI was 24 months (range, 0 to 98); 4 of the patients had a DFI of zero. Twenty-three (69%) of the women were more than 1 year postmenopausal, and only one patient was actively menstruating when placed on study. Sixteen (60%) were more than 5 years postmenopausal. The ERP had been determined and was considered positive by the laboratory performing the test for 19 of the 26 patients. However, only 14 of these had an ERP measured as 10 fmol/mg cytosol protein or more.

Four of the patients in the nonrandomized trial responded: 15% of all eligible and evaluable patients and 11% of all patients treated. Two of these had partial responses in bone, and the other 2 had partial responses in skin. In addition, 4 of the patients classified as nonresponders had stabilization of disease. These responses did not appear to correlate with parameters usually predictive of a response to endocrine therapy. Only 2 of the 14 patients with an ERP of 10 fmol/mg or greater responded; one of the 10 patients who had responded previously to tamoxifen and neither of the 2 patients who had responded previously to both tamoxifen and other endocrine therapy responded to the tamoxifen-aminoglutethimide combination. Similarly, only 2 of the 16 patients who were more than 5 years postmenopausal responded, and all of the responses were among those patients who had had previous chemotherapy, i.e., among those who had had the most prior therapy.

Randomized Study. To date, 26 patients have been entered into the randomized trial. Four of these patients were ineligible, one in each group because they had no measurable disease and 2 patients on the tamoxifen therapy because they had received endocrine therapy previously. In addition, one patient in each treatment group was ineligible, in one case because the patient had just been entered into the trial (less than 1 month) at the time of analysis and in the other because the patient had been taken off therapy at 2 weeks due to toxicity.

The pretreatment characteristics of the 20 eligible and evaluable patients are shown in Table 1. The differences in response are not statistically significant between the 2 treatment groups, although with so few patients even a difference between 27 and 78% would not reach statistical significance. As might be expected from the eligibility requirements, these patients have had less prior therapy than the nonrandomized patients had before entering the trial. In addition, the randomized patients have had metastases for a shorter period of time. Two of the patients were premenopausal (actively menstruating); one was assigned to the tamoxifen arm, and the other, to
the combination. Eleven (55%) had an ERP in excess of 10 fmol/mg; only 5 were ERP unknown. All of these 5 patients had a DFI in excess of 2 years, none had liver or lung involvement, and 4 of the 5 were more than 5 years postmenopausal.

Seven of these patients have responded, 4 to the tamoxifen-aminoglutethimide combination and 3 to tamoxifen alone (Table 2), giving response rates of 36 and 33%, respectively. An additional 5 patients had stabilization of their disease. Neither the percentage of patients responding nor the interval of time to treatment failure (Chart 1) is significantly different for patients in the 2 study groups; however, the time to treatment failure was significantly longer for patients treated on the randomized study when compared to patients treated in the nonrandomized trial. The response rate of patients with an ERP greater than 10 fmol (3 of 11) was not significantly greater than the response rate in other patients. The response rate of patients who were more than 5 years postmenopausal (5 of 13) was not significantly greater than the response rate in other patients. The response rate of patients who were more than 5 years postmenopausal (5 of 13) was not significantly greater than the response rate among pre- and perimenopausal patients. Finally, the response rate among patients with no prior therapy (5 of 10) was only slightly better than that of patients with prior therapy. These significances may change as more patients are accrued.

Responses were seen in breast (1), lymph nodes (2), skin (3), and bone among patients on the 2 different treatment programs. No patients with lung metastases were entered into the trial, and although 4 patients had liver involvement, there was no evidence of response at that site. Serum carcinoembryonic antigen levels were carefully monitored in both the randomized and the nonrandomized trials, but this parameter was not used to score a response. However, this test was useful in confirming response among the 28 patients with baseline carcinoembryonic antigen levels greater than 5. In all cases, the change (or lack of change) in the carcinoembryonic antigen level was in accord with change or stabilization of disease at other sites.

The toxicity observed in patients treated with the combination of tamoxifen-aminoglutethimide was not qualitatively or quantitatively different from that observed in published series in which aminoglutethimide was used as a single agent (21). Four patients discontinued the combination therapy because of toxicity, 2 because of rash and 2 because of confusion and somnolence. Of the patients who continued treatment, 9 developed symptoms of lethargy, 6 had increased fatiguability, and one became depressed. Six patients had mild nausea or vomiting, 3 developed a rash, and 2 had moderate to severe thrombocytopenia. Four developed mild Cushing's syndrome during therapy. Eighteen patients had no toxicity. Patients on tamoxifen alone had frequent but milder side effects, including postmenopausal bleeding (2), confusion and ataxia (3), mild fever (2), transient urinary frequency (2), and, in individual patients, alopecia, anorexia, and nausea. Four patients on tamoxifen alone had no symptoms attributable to drug.

Serial total estrogen and aminoglutethimide levels have been determined for 28 of the patients treated with the tamoxifen-aminoglutethimide combination; 4 of these were responders, and 24 were nonresponders. The mean nadir estrogen level was 24 ± 19 (S.E.) pg/ml in the responders and 42 ± 7 pg/ml (p = 0.17) in the nonresponders. The maximum percentage of decrease in estrogen was 82 ± 10 in the responders and 57 ± 11 in nonresponders (p = 0.20). The peak aminoglu-
tethimide levels averaged 2.8 ± 0.6 µg/ml in responders and 4.2 ± 0.5 µg/ml in nonresponders (p = 0.14).

The median estrogen levels for patients treated with tamoxifen-aminoglutethimide fell steadily over the course of treatment (Charts 2 and 3). The maximum fall was not seen until the sixth to eighth weeks following initiation of therapy. However, by the end of the second week and before full doses of aminogluthethimide had been given, the average estrogen level was 25% (nonrandomized) to 50% (randomized) below pretreatment values. In the randomized study, estrogen levels were significantly lower in patients treated with tamoxifen-aminoglutethimide when compared with the levels in patients treated with tamoxifen alone. This was seen at each sampling point after each therapy was begun (Chart 3).

No statistically significant correlation was observed between the plasma aminoglutethimide level and the total estrogen level (Chart 4). This was true at each testing point during the first 3 months of therapy and regardless of the dose of aminogluthethimide given. In addition, there was no statistically significant relationship between the probability of a clinical response and either the nadir estrogen level, maximum fall in total estrogen from baseline, or peak aminoglutethimide levels of the patient.

Only 3 women were actively menstruating at the time they entered these studies, although four others were perimenopausal with elevated base-line estrogen values. This number is too small to generalize about the effects of these therapies on menstrual function. One patient, aged 41, who had been treated previously with both tamoxifen and chemotherapy, continued to menstruate without noticeable changes in either the periodicity or the duration of menses and without hot flashes throughout the 5 months she received the tamoxifen-aminoglutethimide combination. A second patient, aged 26, who had had prior adjuvant chemotherapy without disruption of menses, had no further menses after her first dose of the combination treatment and reported hot flashes throughout her 3-month course. The third premenopausal patient, given tamoxifen only, was 41, and the interval between her menses lengthened gradually during her 4-month course. She had hot flashes, and her menses ceased permanently during the last 2 weeks of therapy. The patient treated with tamoxifen only had a rise in her total estrogen level which persisted over the last month of therapy, while the 2 premenopausal patients treated with the combination had a transient increase and then a fall in total estrogens (Chart 5).

Discussion

In the nonrandomized study reported here, the response rate to a combination of tamoxifen-aminoglutethimide among women treated previously with tamoxifen was only 15%, and the median time to treatment failure was 3 months. This re-

Chart 2. Aminoglutethimide-tamoxifen patients with prior tamoxifen exposure. Numbers of patients at Weeks 0, 2, 4, 6, 8, and 12 were 21, 19, 15, 12, and 8, respectively. Estrogen suppression was variable and reached statistically significant proportions for the group only at Week 6.

Chart 3. Tamoxifen-aminoglutethimide (TAM/AG) randomized trial. Estrogen level plotted as a function of pretreatment values in patients on tamoxifen (TAM) alone and in patients on tamoxifen-aminoglutethimide. For tamoxifen patients, numbers tested at Weeks 0, 2, 4, 6, 8, and 12 were 7, 5, 6, 4, 6, and 4, respectively. For tamoxifen-aminoglutethimide patients, numbers tested at Weeks 0, 2, 4, 6, 8, and 12 were 7, 5, 6, 4, 5, and 6, respectively. The p value for difference at Weeks 2, 4, 6, 8, and 12 was <0.005, 0.025, 0.04, 0.0005, and 0.005.

Chart 4. Relationship between plasma aminoglutethimide level and plasma total estrogen level. Linear plot of plasma estrogen level against plasma aminoglutethimide level showing no correlation between the variables.
response rate is lower than that reported in earlier Phase II trials utilizing aminoglutethimide alone (21, 22). It is highly unlikely that this combination will prove superior to aminoglutethimide alone in this group of patients, and it cannot be recommended as standard therapy in this setting. However, the frequency and duration of prior endocrine therapy and chemotherapy in this group of patients may be important factors in reducing the response rates to the combination.

Patients who had responded previously to tamoxifen, who had an ERP value greater than 10 fmol/mg, or who were more than 5 years postmenopausal did not respond more often than did other patients, although patients with these characteristics are usually considered preferential candidates for endocrine therapy (5, 6). However, these selection criteria are based upon pretreatment variables and subsequent response rates reported for patients receiving only their first or second therapy. Our patients in the nonrandomized study were more heavily pretreated. For example, only 3 of the 10 patients who had responded previously to tamoxifen had received no other therapy prior to entry into this protocol. This is consistent with a recent report that endocrine therapy responders had response rates of only 30% then 16% to their third and fourth sequential endocrine therapy (10).

Patients entered in the randomized trial had not been pretreated so extensively. However, the data are preliminary. Although there is no clear difference in response rates, it is possible that one or the other treatment program could prove superior with greater patient accrual. We have calculated that 98 patients will be needed to provide an 80% chance of detecting a 25% difference in response rates.

It has been reported previously that, in some premenopausal patients, tamoxifen treatment may induce a rise in circulating estrogen levels (14), but the clinical importance of this observation is not certain. Premenopausal patients clearly respond to tamoxifen; in fact, the response rate to tamoxifen among premenopausal women may be as great as their response rate to oophorectomy (16). It is of interest, however, that the single premenopausal patient in this study who received tamoxifen alone had an elevation of her circulating estrogen level and that the 2 premenopausal patients treated with the combination of tamoxifen-aminoglutethimide had a transient elevation and then a fall in total estrogens, not unlike that observed in postmenopausal patients treated with the combination. If this proves to be a reproducible observation, it may be important. However, it should be emphasized that bloods were drawn without regard to the wide fluctuation in estrogen levels that occurs in the normal menstrual cycle. Tamoxifen elicits the release of gonadotropins which may stimulate responsive ovaries resulting in increased ovarian estrogen secretion (17). Certainly, in ovulating women, chronic administration of aminoglutethimide is ineffective in reducing estrogen levels because of the induced increase in luteinizing hormone secretion (17). Therefore, it is reasonable to suppose that aminoglutethimide would be incapable of inducing remissions in premenopausal patients with breast cancer through this mechanism (17).

Plasma aminoglutethimide levels in patients under chronic treatment did not correlate grossly with plasma total estrogen levels, confirming a previous report (18). In addition, there was no relationship between aminoglutethimide levels and the probability of a clinical response, raising the possibility that lower doses of aminoglutethimide may be as effective as the current standard doses in inducing breast cancer regression. Since most of the toxicity of aminoglutethimide, especially the central nervous system toxicity, is dose related (18), it is plausible that the therapeutic index of this drug might be increased by a reduction of dosage or by using the more potent D enantiomer.

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therapies such as adrenalectomy, it appears to be a useful addition to our therapeutic options. The challenges now are to define dosages, identify related compounds with more potency and fewer side effects (such as D-aminogluthethimide), and, perhaps most important of all, select those patients who would be most likely to achieve a useful response to the treatment.

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