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Progress Report on Two Clinical Trials in Women with Advanced Breast Cancer. Trial I: Tamoxifen *versus* Tamoxifen plus Aminoglutethimide; Trial II: Aminoglutethimide in Patients with Prior Tamoxifen Exposure[1]

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Abstract

A progress report is presented on two on-going clinical trials in women with advanced breast cancer. In Trial I to date, 56 patients have been randomized to tamoxifen (TAM) alone or TAM plus aminoglutethimide (AG) (plus hydrocortisone). Patients failing TAM can then receive AG. The two groups are reasonably well balanced with respect to prior hormonal therapy exposure (TAM, 19%; TAM plus AG, 17%), age, disease-free interval, performance score, and estrogen receptor status. The TAM plus AG group has a higher incidence of visceral dominant disease (41 *versus* 26%) and prior chemotherapy exposure (41 *versus* 33%). Responses have been observed in 7 of 27 (26%) patients on TAM and 11 of 28 (39%) on TAM plus AG. Median times to treatment failure (defined as disease progression, unacceptable toxicity, or patient refusal) are 211 and 123 days, respectively (log-rank on time to treatment failure, $p = 0.87$). Toxicity is greater for TAM plus AG with a higher incidence of skin rash, lethargy, and dizziness. Thrombotic events were seen in one patient on TAM and two patients on TAM plus AG. One patient on TAM plus AG developed leukopenia and sepsis. The data are too preliminary for one to draw firm conclusions regarding relative efficacy.

In Trial II to date, 35 patients with prior tamoxifen exposure have received AG. The mean number of prior systemic therapies is 3.2 (range, 1 to 7). The response rate is 20% and similar with (21%) or without (19%) prior chemotherapy exposure. The median time to treatment failure is 92 days. One patient developed leukopenia and sepsis. Additional patient accrual is necessary to allow characterization of potential efficacy within prognostically important subsets.

Introduction

Tamoxifen is currently considered to be the hormonal agent of choice in postmenopausal (5 or more years since last menstrual period) women with advanced carcinoma of the breast (2). Although apparently less effective in paramenopausal (1 to less than 5 years since last menstrual period) and castrated women, tamoxifen has produced a 26% objective response rate in a group of such patients (3). It appears to compete with estradiol for the estrogen receptor (1).

Aminoglutethimide has also been reported to produce objective regressions in advanced breast cancer (9). Its mechanism of action appears to be a decrease of endogenous estrogens by blockade of adrenal steroidogenesis as well as blockade of peripheral aromatization of androstenedione to estrone (9).

The use of tamoxifen plus aminoglutethimide in women with advanced breast cancer is considered to be a dual approach involving the decrease of estrogen levels with aminoglutethimide, thus possibly allowing tamoxifen to compete more effectively with estradiol at the cellular level. To determine relative efficacy of this combined approach, a randomized clinical trial is being performed comparing tamoxifen plus aminoglutethimide with tamoxifen alone (Trial I). Because many women have received prior tamoxifen therapy and thus are ineligible for the randomized trial, a Phase II study of aminoglutethimide is also in progress (Trial II).

Materials and Methods

Ninety-one patients with histological confirmation of breast cancer and progressive metastatic disease have been entered into these 2 trials since April 1980 (Trial I, 56 patients; Trial II, 35 patients). Eligibility requirements include a paramenopausal, postmenopausal, or castrated status. Women who have undergone a hysterectomy without oophorectomy must be at least 50 years old. An indicator lesion must be present, *i.e.*, either measurable or evaluable (*i.e.*, assessable but not measurable). Estrogen receptor data are not mandatory for entry into this study, but when available, are required to be positive (defined as greater than 3 fmol of receptor per mg of cytosol protein by a dextran-coated charcoal technique). Estrogen receptor data are used only if no systemic anticancer therapy has intervened between its determination and entry into the study. Patients are required to have an Eastern Cooperative Oncology Group performance score (2) of 3 or better. Serum calcium must be less than 12 mg/dl, creatinine less than or equal to 1.5 mg/dl, and total bilirubin less than 2 mg/dl. Patients are not eligible for either trial if they have received prior aminoglutethimide. Patients without prior tamoxifen exposure are eligible for the randomized Trial I, while those with prior tamoxifen exposure are eligible for Trial II.

Studies obtained prior to entry on protocol include a history, physical examination, WBC, platelet count, chemistry profile, metastatic bone survey, free and total serum thyroxine, and serum dehydroepiandrosterone sulfate.

For Trial I, patients are stratified according to estrogen receptor status (positive *versus* unknown), Eastern Cooperative Oncology Group performance score (0 to 1 *versus* 2 to 3), prior hormonal therapy (yes *versus* no), prior chemotherapy (yes *versus* no) and dominant disease status (soft tissue, osseous, visceral). Patients are then randomized, using the Pocock-Simmon (8) approach to adaptive randomization, to treatment with either tamoxifen or tamoxifen plus aminoglutethimide plus hydrocortisone. The dosage of tamoxifen is 10 mg by mouth twice daily. The dosage of aminoglutethimide (supplied as Cytadren by CIBA-

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GEIGY Corp., Summit, N. J.) was initially 250 mg 4 times daily but was modified after the initial entry of 3 patients on each treatment regimen to an induction dosage of 125 mg 4 times daily for the first 2 weeks and then 250 mg 4 times daily thereafter. This change was based on excessive lethargy observed with the higher dose and on data showing that aminoglutethimide increases its own metabolism (7). Hydrocortisone is administered p.o. at a dose of 100 mg daily (8 a.m., 20 mg; 2 p.m., 20 mg; 5 p.m., 60 mg) for the first 2 weeks and then 40 mg daily (8 a.m., 10 mg; 5 p.m., 10 mg; at bedtime, 20 mg) thereafter.

For Trial II, patients are registered and treated with aminoglutethimide and hydrocortisone with the dosages and schedules as listed above.

All patients are assessed 1 month after therapy is begun and every 1 to 2 months thereafter. Treatment is continued if a patient's status is stable or better and if no unacceptable toxicity has occurred. Response criteria for patients with measurable indicator lesions are those traditionally used and previously reported (4). For patients with evaluable indicator lesions, regression is defined as a definite decrease in tumor size, and progression is defined as the appearance of a new lesion or definite increase in tumor size. Treatment failure is defined as progression of disease, appearance of unacceptable toxicity, or refusal of the patient to continue the treatment program. The best response of patients in whom treatment failure occurs without progression of disease is taken to be that achieved prior to removal from treatment. In the analysis of time to progression, patients who are declared to have treatment failure without disease progression are censored at the time of treatment failure. In Trial I, patients who experience treatment failure on tamoxifen alone and are still clinically considered candidates for hormonal therapy are offered therapy with aminoglutethimide.

For this progress report, regression data were examined using contingency tables. Data on treatment failure, progression, and survival were examined using log-rank tests (6) and Kaplan-Meier estimation (5).

Results

Trial I: Tamoxifen versus Tamoxifen plus Aminoglutethimide

Patient Characteristics. The 2 study groups are reasonably well balanced with respect to most pretreatment patient characteristics listed in Table 1. The tamoxifen plus aminoglutethimide group has a higher incidence of visceral dominant disease and prior chemotherapy exposure. In those patients with prior systemic therapy, the mean number of prior regimens is 1.5 in both groups.

Response Data. Response data are available for 55 patients (Table 2). The proportions of patients with a response (tamoxifen, 26%; tamoxifen plus aminoglutethimide, 39%) are not significantly different between the 2 groups ($p = 0.29$, χ^2 test). However, due to the fact that the study is ongoing and the best response may not yet have been achieved in all patients, the response probabilities are underestimated, and therefore the reported p value is approximate.

Response rates according to dominant disease status for tamoxifen and tamoxifen plus aminoglutethimide are 43 and 50%, respectively, in soft tissue dominant disease; 15 and 27%, respectively, in osseous dominant disease; and 29 and 45%, respectively, in visceral dominant disease. Considering estrogen receptor-positive patients only, 5 of 13 (38%) patients receiving tamoxifen and 6 of 14 (43%) patients receiving tamoxifen plus aminoglutethimide have achieved an objective response.

Treatment Failure and Progression. To date, treatment failure has occurred in 63% of patients receiving tamoxifen and 68% of patients receiving tamoxifen plus aminoglutethimide. Median times to treatment failure (Chart 1) by the Kaplan-Meier method are 211 and 123 days, respectively. The log-rank test of equality of treatment failure distributions does not show a significant difference ($p = 0.87$). The median times to progression are 216 and 157 days, respectively. The log-rank test of time to progression distributions, likewise, does not show a significant difference ($p = 0.85$).

Survival. Thus far, only 2 patients on tamoxifen and 5 patients on tamoxifen plus aminoglutethimide have died.

Secondary Treatment Phase. Eleven patients have received aminoglutethimide immediately after failure on tamoxifen. The best prior response to tamoxifen in these 11 patients had been partial regression in 4, stabilization in 4, and immediate progression in 3. Only 1 (9%) patient (a prior tamoxifen responder) has achieved an objective response with aminoglutethimide and all but 2 of the 11 patients have had subsequent progression.

Table 1

Pretreatment patient characteristics for trial of tamoxifen versus tamoxifen plus aminoglutethimide

	Tamoxifen	Tamoxifen + aminoglutethimide
No.	27	29
Age (yr)		
Median	59.5	56.5
Range	38–83	41–79
Disease-free interval		
<1 yr	9 (33)[a]	8 (28)
1–5 yr	11 (41)	11 (38)
>5 yr	7 (26)	10 (34)
Eastern Cooperative Oncology Group performance score		
0–1	25 (93)	26 (90)
2–3	2 (7)	3 (10)
Estrogen receptor		
Positive	13 (48)	15 (52)
Unknown	14 (52)	14 (48)
Dominant disease status		
Soft tissue	7 (26)	6 (21)
Osseous	13 (48)	11 (38)
Visceral	7 (26)	12 (41)
No prior systemic therapy	16 (59)	15 (52)
Prior hormonal therapy	5 (19)	5 (17)
Prior chemotherapy	9 (33)	12 (41)

[a] Numbers in parentheses, percentage.

Table 2

Response data for trial of tamoxifen versus tamoxifen plus aminoglutethimide

Indicator lesion	Tamoxifen	Tamoxifen + aminoglutethimide
Measurable		
Partial regression	7/22 (32)[a]	8/18 (44)
Stable	10/22 (45)	9/18 (50)
Immediate progression	5/22 (23)	1/18 (6)
Evaluable (Nonmeasurable)		
Regression	0/5 (0)	3/10 (30)
Stable	4/5 (80)	6/10 (60)
Immediate progression	1/5 (20)	1/10 (10)
Responses (Partial regression + regression)	7/27 (26)	11/28 (39)

[a] Numbers in parentheses, percentage.

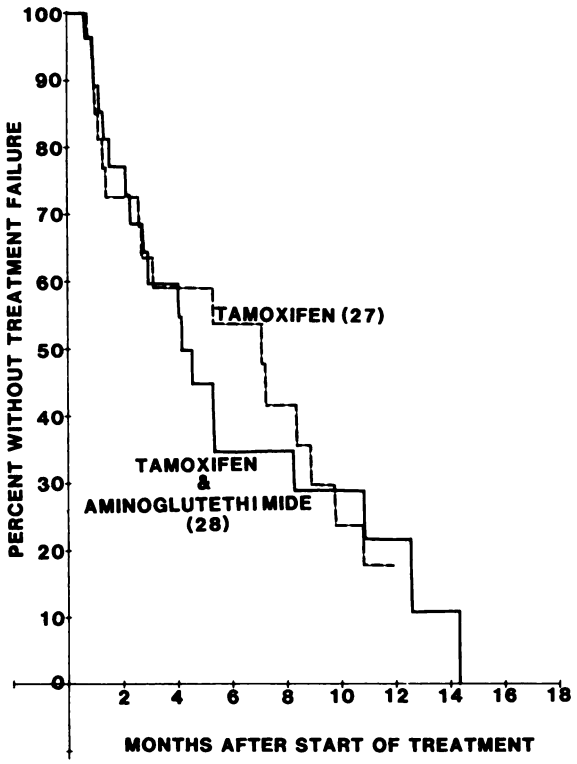

Chart 1. Time to treatment failure for patients receiving tamoxifen and tamoxifen plus aminoglutethimide.

Toxicity. Toxicities are listed in Table 3. The 3 initial patients treated with higher-dose aminoglutethimide are not included. In addition to the toxicities listed, untoward episodes have occurred on both treatment arms. On the tamoxifen-only arm, one patient refused further therapy because of multiple systemic complaints including lethargy and increased pain, which cleared after discontinuing the tamoxifen, and another patient developed an arterial occlusion in her right leg. With tamoxifen plus aminoglutethimide, 5 (18%) patients have had treatment failure without disease progression: 1 with leukopenia (WBC = 600/cu mm) and sepsis which resolved after discontinuation of the aminoglutethimide; 1 with pulmonary embolus; 1 with lower extremity thrombophlebitis; 1 with an extensive persistent skin rash; and 1 with urticaria and laryngeal edema.

Eighteen patients on tamoxifen plus aminoglutethimide have a baseline free and total serum thyroxine determination and at least one follow-up determination, and one patient has developed a free thyroxine level below the normal range.

Trial II: Aminoglutethimide in Patients with Prior Exposure to Tamoxifen

Patient Characteristics (Table 4). This group of patients by definition all had received prior hormonal therapy, and most had received multiple prior systemic therapies (median, 3.0; mean, 3.2; range, 1 to 7).

Response Data. Response data are available on 35 patients. The best response achieved is partial regression in 6 (20%) of 30 patients with measurable disease and 1 (20%) of 5 with evaluable disease. The response rate is similar whether the patient had (21%) or did not have (19%) prior chemotherapy exposure. Fourteen patients had received tamoxifen as the treatment immediately prior to aminoglutethimide. In 11 of these 14 patients, the best response achieved with tamoxifen was known and was objective response in 6, stable in 3, and immediate progression in 2. Only 1 (9%) of these 11 patients has achieved an objective response (a partial regression), and all others have subsequently experienced treatment failure. Five patients had an objective response to a hormonal manipulation other than tamoxifen immediately prior to treatment with aminoglutethimide, and one patient has achieved an objective response (partial regression) with aminoglutethimide. The hormonal manipulations which immediately preceded the aminoglutethimide treatment in these 5 patients were megestrol acetate in 2 patients and diethylstilbestrol, diethylstilbestrol withdrawal, and an oophorectomy in one patient each.

Table 3

Toxicities observed during trial of tamoxifen versus tamoxifen plus aminoglutethimide

	Tamoxifen (27 patients)		Tamoxifen + aminoglutethimide (25 patients)	
	No.	%	No.	%
Nausea	4	15	6	24
Emesis	2	7	3	12
Fever	0	0	3	12
Skin rash	1	4	11	44
Lethargy	7	26	15	60
Dizziness	3	11	8	32
Ataxia	2	7	5	20
Leg cramps	3	11	6	24
Edema	3	11	4	16
Facial fullness	1	4	8	32
Hot flushes	13	48	12	48

Table 4

Pretreatment patient characteristics for trial of aminoglutethimide

No.	35
Age (yr)	
Median	59
Range	32–81
Disease-free interval	
1 yr	6 (17)[a]
1–5 yr	21 (60)
5 yr	8 (23)
Eastern Cooperative Oncology Group performance score	
0–1	22 (63)
2–3	13 (37)
Estrogen receptor	
Positive	8 (23)
Unknown	27 (77)
Dominant disease status	
Soft tissue	6 (17)
Osseous	13 (37)
Visceral	16 (46)
Prior chemotherapy	14 (40)

[a] Numbers in parentheses, percentage.

Treatment Failure and Survival. Thirty-four patients have had treatment failure (3 due to toxicity, 1 refusal, 1 death, 30 progression). Median time to treatment failure is 94 days. Eight (23%) patients have died.

Toxicity. Toxicities are listed in Table 5. The initial 3 patients treated with a higher dose of aminoglutethimide are not included. Three patients were removed from treatment because of toxicity without disease progression, one with persistent fever and chills, one with leukopenia (WBC = 600/cu mm) and sepsis which resolved after discontinuation of the aminoglutethimide, and one with a picture of frank Addisonian crisis. In

Table 5
Toxicities observed with aminoglutethimide

	Aminoglutethimide + hydrocortisone (32 patients)	
	No.	%
Nausea	7	22
Emesis	5	16
Fever	5	16
Skin rash	8	25
Lethargy	17	53
Dizziness	10	31
Ataxia	5	16
Leg cramps	7	22
Edema	6	19
Facial fullness	9	28
Hot flushes	11	34

addition, one patient who had been stable died suddenly at home on Day 86 of treatment, but no autopsy was obtained.

Twenty-seven patients have a baseline free and total serum thyroxine determination and at least one follow-up determination, and 5 (19%) have developed a free thyroxine below the normal range.

Discussion

The data are too preliminary for one to draw conclusions regarding the relative efficacy of the tamoxifen and tamoxifen plus aminoglutethimide regimens. The results observed and the relatively small number of patients preclude ruling out anything but very large differences in response rates or time to treatment failure. Likewise, further assessment is necessary to establish the role, if any, for aminoglutethimide after tamoxifen therapy since other therapeutic options exist; *e.g.*, diethylstilbestrol has, in our experience, produced a 45% objective response rate in prior tamoxifen responders (2). Aminoglutethimide has produced objective responses in patients with multiple prior systemic therapy exposures (Trial II in this report), but additional patient accrual is necessary to allow characterization of response probabilities within prognostically important subsets.

Of the greatest concern in this study is the occurrence of life-threatening and fatal events, namely, profound leukopenia and thromboembolic phenomena. The association of leukopenia with aminoglutethimide has been reported (10) and has occurred in this study in one patient each on both the aminoglutethimide and tamoxifen plus aminoglutethimide regimens. The 2 patients in our series presented with sepsis on Days 57 and 67 of therapy and gave a history of recent (within 1 week) onset of diarrhea; both had had a normal WBC count prior to therapy and at the 1-month assessment. It is important for investigators to keep this complication in mind, especially if a patient develops a new fever, signs of infections, or diarrhea after the first month of aminoglutethimide therapy.

Thrombotic phenomena occurred with both the tamoxifen and tamoxifen plus aminoglutethimide regimens. In addition, the sudden death of a patient on aminoglutethimide who had been doing well clinically raises the possibility of a thromboembolic event. Further close scrutiny for such events is required.

The occurrence of toxic reactions such as fever, lethargy, and skin rash raise concern regarding the use of aminoglutethimide in the early stages of hormonal management, especially when a relatively nontoxic agent such as tamoxifen is available. In most patients treated with aminoglutethimide, whether alone or with tamoxifen, these toxicities will resolve without cessation of therapy. In our experience, however, there are some patients who cannot tolerate aminoglutethimide.

The concepts inherent in the mechanism of action of aminoglutethimide are innovative and important to pursue as are those of the dual approach using tamoxifen plus aminoglutethimide. However, it appears that less toxic means of accomplishing the same ends should be sought.

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Discussion

Dr. Gale: Dr. Powles, did you see any SIADH[1] responses in the patients who were on the TAD regimen with danazol?

Dr. Powles: No. Now let me make an additional comment. The criteria for patients who were randomized to the 2 groups were the same for age, receptor status, and I think it was 57 to 63% ER positive for the TAD and for the TAM. The response rate was about the same for the patients who were receptor positive with TAD and for those with TAM.

Dr. Harvey: If you will permit me to summarize data presented in abstracts, I am trying to get at the question of the relative roles of these 2 active agents, AG and TAM. I have reviewed the data presented by Drs. Henderson, Harris, Ingle, Murray, Buzdar, Harvey, and Ragaz, and I have come up with a total of 262 patients who were treated with AG and 85 of them who have had an objective response, for an overall response rate of 30.2%. If one looks at patients who receive AG after having responded to TAM, the overall response rate is 50%. Next, if one looks at the TAM nonresponders who get AG, the subsequent

[1] The abbreviations used are: SIADH, Syndrome of Inappropriate ADH Secretion; TAD, tamoxifen-aminoglutethimide-danazol; ER, estrogen receptor; TAM, tamoxifen; AG, aminoglutethimide; FAC, 5-fluorouracil + Adriamycin + Cytoxan.

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