Cross-Over Comparison of Tamoxifen and Aminogluthimide in Advanced Breast Cancer

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Abstract

Thirty-four postmenopausal patients with advanced breast cancer had an overall objective response rate of 47% when treated with aminogluthimide and hydrocortisone initially and a response rate of 24% when crossed over to therapy with tamoxifen after progression on aminogluthimide. A similar group of 32 patients experienced a response rate of 28% when treated with tamoxifen first and a 19% objective response rate on subsequent therapy with aminogluthimide. Patients who failed to respond to the first therapy seldom responded on cross-over to the alternate therapy. Toxicities were acceptable with both forms of therapy. Tamoxifen and aminogluthimide used sequentially are effective forms of palliative hormonal therapy in metastatic breast cancer.

Background

Hormonal treatment remains a simple, safe, and highly effective means of palliative management of advanced breast cancer, especially in patients with estrogen receptor-rich tumors (2). One mechanism by which an endocrine treatment of breast cancer may work is to deprive the hormone-dependent cell of estrogen. This may be achieved by administering the antiestrogen tamoxifen, which competes with estrogen for binding to its specific receptor. Tamoxifen has become an established form of therapy in clinical practice (3). An alternative nonsurgical method of achieving estrogen deprivation in the postmenopausal patient is to block the synthesis of estrogen precursors in the adrenal gland as well as to inhibit the aromatase enzyme responsible for the conversion of androgens to estrogens in peripheral tissues (8). We have reported this mechanism of action previously and the considerable efficacy of a combination of aminogluthimide and hydrocortisone in the treatment of advanced breast cancer (5, 6).

The current study was undertaken to ascertain whether postmenopausal patients with metastatic breast cancer first treated with tamoxifen would later respond to aminogluthimide and vice versa and to determine if there should be a preferred sequence of administering these 2 agents in clinical practice. This study was begun in April 1977.

Materials and Methods

Patients. Sixty-six postmenopausal patients with metastatic breast carcinoma were selected for study. All patients had measurable disease, and some had received prior hormonal therapy or chemotherapy but not in the 4 weeks immediately preceding entry to the study. Patients were entered on the study at a time when their disease was felt to be progressive and after they had given informed consent.

Prior to entry into the trial and at 3-month intervals until progression, studies consisted of a history, physical examination, complete blood count, chest X-ray, bone scan, skeletal survey, liver scan, liver function studies, and photography and measurement of all lesions.

Only patients whose tumors were estrogen receptor unknown or estrogen receptor positive (>10 fmol/mg cytosol protein by dextran-coated charcoal assay) were eligible for this study. Posttreatment biopsies for redetermination of estrogen receptors were obtained in a few patients. Patients with disease involving greater than one-third of the liver were excluded from the study as were patients with lymphangitic spread of tumor to the lungs, hypercalcemia, or neurological involvement by breast carcinoma.

Treatment Schedules. Patients were assigned to receive a regimen of either aminogluthimide and hydrocortisone or tamoxifen. When disease progression became apparent, patients were crossed over to the alternative regimen. Patients who had responded initially to tamoxifen and later progressed were left untreated for a period of 2 to 4 weeks to observe for a withdrawal response.

Aminogluthimide (Cytadren; CIBA-GEIGY Corp., Summit, N. J.) was administered in a starting dose of 250 mg p.o. twice a day for 2 weeks and then increased to 250 mg p.o. 4 times a day. Hydrocortisone was given concomitantly in an initial dose of 100 mg in a divided daily dose (60 mg at bedtime, 20 mg every morning, 20 mg every day at 5 p.m.) and after 14 days decreased to 50 mg daily (20 mg at bedtime, 10 mg every morning, 20 mg at bedtime). Tamoxifen (Nolvadex; Stuart Pharmaceuticals) was initially administered in a dose of 20 mg p.o. twice a day, but in the last year of the study, this has been reduced to 10 mg p.o. twice a day.

Response Criteria. Complete objective tumor regression required the disappearance of all measurable lesions and/or the recalcification of all lytic lesions in bone for at least 3 months. Partial objective regression represented a 50% decrease in the sum of products of all measurable lesions and/or recalcification of lytic lesions without simultaneous appearance of new lesions. The stable category arbitrarily included only patients with isolated bone lesions, who developed no new lesions on bone X-rays and also experienced subjective relief of bone pain for a period of 6 months or greater during therapy. Patients with skin, soft tissue, or visceral lesions which did not regress by 50% at any time during observations were arbitrarily considered to have progressive disease. In any patient with the appearance of a new lesion during treatment or with an increase in the sum of products of measurable disease of greater than 25%, the disease was called progressive. Duration of regression included the time interval between the initiation of therapy and the first documentation of disease progression.

The general characteristics of the study population are summarized in Table 1.

Results

The objective response rate of 47% in 16 of the 34 patients initially treated with aminogluthimide and hydrocortisone ac-
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records with our experience in a larger group of patients (7). Thirteen % of these patients had stable disease, and the median duration of response was 18 months. The 28% objective response rate among the 32 patients first treated with tamoxifen is somewhat lower than is generally reported in the literature. This may be accounted for in part by a preponderance of patients with bone involvement who could be scored only as having stable disease (28% in this group). These results are summarized in Table 2.

The cross-over data show a response rate of 24% for tamoxifen as second therapy with 21% stabilizations. The objective response rate among patients crossed over to aminoglutethimide was 19% with 22% stabilizations (Table 3). Four of 9 patients who responded initially to tamoxifen responded subsequently to aminoglutethimide, and of the 16 aminoglutethimide responders 5 subsequently responded to tamoxifen. Five patients on cross-over therapy had stabilization of disease. Only 2 of 11 evaluable patients who had failed to respond to aminoglutethimide had an objective response on tamoxifen, and only one of 14 tamoxifen-resistant patients subsequently responded to aminoglutethimide. These results are summarized in Table 4.

Toxicity seen with aminoglutethimide and tamoxifen on this study was similar in frequency to that which we have reported previously (1, 7). Toxicity on tamoxifen included tumor flare in 3 patients, significant nausea and vomiting in 3 patients, and deep-vein thrombophlebitis in one patient. Therapy was discontinued in 2 patients because of side effects. Toxicities for aminoglutethimide included skin rash in 9 patients, drug fever in 3, lethargy and dizziness in 7, and pancytopenia in one patient. Therapy had to be discontinued in 3 patients because of side effects.

Discussion

The sequential use of endocrine therapies in an individual patient with advanced hormone-dependent breast cancer affords the clinician the ability to treat that patient for a prolonged period of time with relatively nontoxic therapy. The regimen of aminoglutethimide and hydrocortisone avoids the need for major endocrine ablation while producing marked suppression of estrogen synthesis (3, 4). The major action of aminoglutethimide appears to depend on its role as a potent inhibitor of aromatase. Tamoxifen blocks estrogen activity by competitive binding to cytoplasmic receptors. This study is ongoing but thus far demonstrates that these 2 different methods of estrogen suppression produce effective palliation when used sequentially. On the other hand, the low response rate to subsequent treatment with either tamoxifen or aminoglutethimide in patients who failed initially to respond to either of these agents (especially if confirmed by studying a larger population) should indicate to the clinician the need to switch to other treatment modalities, e.g., cytotoxic chemotherapy.

In patients with hormone-dependent tumors for whom an ablative form of therapy would be selected, aminoglutethimide might be used as a first alternative. In the majority of patients, however, for practical reasons, tamoxifen would be used as initial treatment, and cross-over to aminoglutethimide would be considered in those patients who were no longer responding to tamoxifen.
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References


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