Clinical Trial of Multiple Endocrine Therapy for Metastatic and Locally Advanced Breast Cancer with Tamoxifen-Aminoglutethimide-Danazol Compared to Tamoxifen Used Alone

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Abstract

Multiple-endocrine therapy with combinations of various types of treatment has not been evaluated properly in spite of the success of individual types of hormone treatment. This paper reports the early results of a randomized controlled clinical trial comparing tamoxifen (10 mg 2 times/day)-aminoglutethimide (250 mg 3 times/day)-danazol (100 mg 3 times/day)-hydrocortisone (20 mg 2 times/day) (TAD) with tamoxifen (10 mg 2 times/day).

Analysis of the first 107 assessable patients indicates objective response (criteria of the International Union Against Cancer) in 33% of patients receiving tamoxifen versus 50% of patients receiving TAD. Duration of response to TAD is identical to duration of response to tamoxifen alone. TAD is well tolerated, and toxicity, although greater than for tamoxifen, is acceptable.

Introduction

Although various types of endocrine therapy have been used successfully to cause remissions of metastatic or locally advanced breast cancer, there have been few reports on treatment with combinations of more than one kind of endocrine therapy. Combinations of androgen with estrogen (6), corticosteroids with radiation menopause (1, 14), androgen with castration (3, 5), estrogen with progesterone (7, 12), and tamoxifen with androgen (20) have been reported with varying degrees of success. Generally, the results, mostly based on noncontrolled clinical studies, have been inconclusive and difficult to interpret.

The variations in distribution of steroid receptors and other prognostic indications of response, together with the dissimilarities in pharmacology and toxicity of each type of treatment, indicate a need for further searching for more successful combinations of endocrine therapy.

Tamoxifen will induce remissions in 30 to 40% of patients with advanced breast cancer with a mean duration of response of 9 to 20 months (8, 11) apparently by a direct antiestrogenic effect on breast cancer cells (9). Similarly, approximately 30% of patients respond to aminoglutethimide (17, 19), an agent which inhibits steroid, particularly estrogen, synthesis by the adrenal and other tissues (10, 13, 18). Another endocrine agent used for treatment of metastatic breast cancer is danazol (2), a synthetic progestin with impeded androgenic properties (15).

This paper reports a controlled randomized clinical trial which compared treatment of advanced breast cancer with tamoxifen to treatment with a combination of TAD.

Patients and Methods

Between September 1979 and April 1981, 122 patients with assessable metastatic or locally advanced breast cancer have been randomized to receive either tamoxifen (10 mg twice/day) or a combination of tamoxifen (10 mg twice/day), aminoglutethimide (250 mg 3 times/day), danazol (100 mg 3 times/day), and hydrocortisone (20 mg twice/day). All patients were at least 1 year postmenopausal, with histologically confirmed breast cancer and with a life expectancy of at least 3 months. None had been treated previously with tamoxifen, aminoglutethimide, danazol, or corticosteroids. Ten patients had had alternative endocrine therapy previously but none for 6 weeks prior to inclusion in this trial. An additional 12 patients had been treated previously with cytotoxic chemotherapy but none for at least 3 weeks prior to randomization for this trial.

Although all patients were assessable for toxicity, only 107 patients (57 tamoxifen versus 50 TAD) were assessable for tumor response at 3 months, either because of early death, intolerable toxicity, life-threatening progression of disease, or disease considered inassessable for response on subsequent review. Assessment of response has been defined for all patients according to criteria of the International Union Against Cancer (4).

Prior to the start of treatment, all patients were assessed for extent and distribution of disease, including full clinical investigation, photography of visible lesions, biopsy if possible for steroid receptor assays, full blood count, iliac crest bone marrow aspiration, liver function tests, serum calcium, bone scan, chest X-ray, radiological skeletal survey, and tomography or computer-assisted tomographic scan if indicated.

All patients were clinically assessed at monthly intervals and continued treatment for at least 3 months. Treatment was stopped if patients had progressive disease, either through failure to respond or at relapse after response or stabilization of disease. All investigations were repeated at 3 months and subsequently at 6-month intervals while on treatment.

Results

Of the 122 patients who had been randomized by April 1981, sixty were allocated to receive TAD and 62, tamoxifen. The mean age, the duration from first relapse to start of tamoxifen or TAD, the proportion estrogen receptor positive, and the number who had received previous systemic treatment were the same for both groups (Table 1). Of the patients who received TAD, 7 achieved CR, 13 had stabilization of disease, and 12 had progressive disease in spite of treatment. Of those receiving tamoxifen, 5 achieved CR, 14 had PR, 13 had stabilization of disease, and 25 had progressive disease (Table 2).
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This gives an overall response rate for all randomized patients of 42% for TAD compared to 31% for tamoxifen, and for assessable patients, 50% for TAD compared to 33% for tamoxifen. An additional 26% of the TAD patients and 23% of tamoxifen patients had stabilization of their disease for at least 3 months, giving an overall success for TAD treatment of 76% compared to 56% for tamoxifen.

The time taken to achieve remission was the same in both groups (Table 3). Remission in bone took longer to achieve (median, 41.5 weeks) than in viscera (CR, 27.5 weeks; PR, 22.5 weeks) or soft-tissue disease (CR, 17.1 weeks; PR, 15.0 weeks). The duration of remission was the same for both groups (Chart 1), although median duration of remission has not yet been achieved.

Survival for the 2 groups of patients at the present time is similar. Twenty-one patients have died in each group, and actuarial life table analysis shows no difference in predicted survival (Chart 2), although the median survival has not been reached.

Both treatments were well tolerated, and treatment was stopped because of intolerance in only one patient receiving TAD and in none receiving tamoxifen. Lethargy, skin rash and Cushingoid symptoms, mild hypercalcemia, and edema were the main problems (Table 4) and generally resolved with dose modification.

Discussion

These results indicate that patients can be treated effectively with TAD multiple-endocrine therapy with an increased response rate compared to that achieved with tamoxifen alone. The duration of response is similar for both types of treatment, but further follow-up is required in order to identify possible benefit for most patients in remission. Similarly, although actuarial life table analysis indicates no difference in survival between the 2 groups, the patients who have died so far are nonresponders to treatment. Whether there is any survival benefit for the increased number of responding patients on TAD or not is not clear from the data presented. Further follow-up is required to determine this question.

Table 1

| Characteristics of patients receiving either tamoxifen or TAD |
|-----------------|-----------------|-----------------|-----------------|
| Total no.       | Mean age (yr)   | Estrogen receptor positive | Previous endocrine therapy | Previous chemotherapy |
| TAD             | 60              | 64              | 7.5            | 9/16 56 7 8 |
| Tamoxifen       | 62              | 66              | 6.7            | 12/19 63 11 4 |

Table 2

| Objective response (criteria of the International Union Against Cancer) for patients receiving either tamoxifen or TAD |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Total no. of patients | No. assessable for response | CR | PR | Stabilization | Progressive disease | % of response (CR + PR) and stabilization of assessable patients |
| TAD              | 60              | 50              | 7 18 | 13 12 42 50 | 76 |
| Tamoxifen        | 62              | 57              | 5 14 | 13 25 31 33 | 56 |

% of response (CR + PR) and stabilization of assessable patients

Table 3

| Time from start of tamoxifen or TAD to achievement of overall PR or CR for those patients who responded to treatment |
|-----------------|-----------------|-----------------|-----------------|
| Time (wk) to response | PR | CR |
| TAD              | 18.24 ± 15.1 (2-52) | 21.6 ± 12.6 (8-49) |
| Tamoxifen        | 20.5 ± 17.7 (5-81) | 21.4 ± 9.1 (12-37) |

a Mean ± S.E.
b Numbers in parentheses, range.
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Table 4
Number of patients having morbidity including toxicity to tamoxifen or TAD

<table>
<thead>
<tr>
<th></th>
<th>Lethargy</th>
<th>Skin rash</th>
<th>Nausea</th>
<th>Hyper-calcemia</th>
<th>Edema</th>
<th>Cushing-oid symptoms</th>
<th>Masculinization, hirsutism</th>
<th>Hot flushes</th>
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</thead>
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<td>23</td>
<td>9</td>
<td>10</td>
<td>4</td>
<td>16</td>
<td>9</td>
<td>5</td>
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<td>Tamoxifen (62)</td>
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<td>0</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Numbers in parentheses, total number receiving treatment.

TAD compared to tamoxifen remains to be seen with longer follow-up.

With the relative failure of cytotoxic drugs for treatment of metastatic breast cancer (16), emphasis is again being directed towards endocrine therapy.

With the variations in types of endocrine therapy available for treatment of metastatic breast cancer, it is surprising that more effort has not been made to evaluate the efficacy of multiple-endocrine therapy. Treatment benefit will probably only be identified by properly controlled clinical trials, and aminoglutethimide with its unique mechanism of action associated with high response rate should be considered for inclusion in future combinations.

References

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