Use of Aminoglutethimide as Second-Line Endocrine Therapy in Metastatic Breast Cancer

Stanley B. Kaye, Robert L. Woods, Richard M. Fox, Alan S. Coates, and Martin H. N. Tattersall

Ludwig Institute for Cancer Research, University of Sydney, Sydney, New South Wales, Australia

Abstract

Sixty-five patients with advanced breast cancer, progressive despite prior endocrine therapy in all cases and prior chemotherapy in most cases, were treated with aminoglutethimide, 250 mg four times a day. At present, 52 are evaluable for response assessment, and of these 10 (19%) showed an overall objective response, major sites of response being soft tissue and lung. A further 12 patients (23%) had stable disease. Therapy in most cases, were treated with aminoglutethimide, despite prior endocrine therapy in all cases and prior chemotherapy. Aminoglutethimide was reasonably well tolerated, although 6 patients (9%) discontinued treatment because of intolerable side effects.

Six of the 10 responding patients have subsequently relapsed, with a mean duration of response of 17 weeks, but 4 continued to respond at 24, 32, 55, and 111 weeks, respectively. The median survival from the start of aminoglutethimide therapy is in excess of 41 weeks for responders and 11 weeks for nonresponders, while the median survival from first relapse is 48 months for aminoglutethimide responders and 28 months for aminoglutethimide nonresponders.

These results confirm that aminoglutethimide can offer a useful alternative form of endocrine therapy for advanced breast cancer, but the response rates obtained in heavily pretreated patients are inferior to those obtained when aminoglutethimide is used earlier in sequential treatment. For optimal results, particularly in terms of quality of life, aminoglutethimide should generally be used prior to chemotherapy.

Introduction

Aminoglutethimide, first developed as an anticonvulsant 20 years ago, has now been shown in several series to be an effective and safe form of endocrine therapy in advanced breast cancer (2, 3, 6, 9, 10, 12). The drug acts by lowering circulating estrogen levels, at least partly by inhibition of peripheral aromatization of androstenedione (9), but its precise role in sequential treatment in relation to other forms of endocrine therapy or chemotherapy is not yet clear.

As with many new drugs, aminoglutethimide may frequently be given to patients after other forms of standard treatment have failed. In this study, almost all the patients receiving aminoglutethimide had previously been included in a multicenter study which included both combination chemotherapy and endocrine therapy (i.e., tamoxifen). It is therefore of interest to establish the efficacy of aminoglutethimide in this common clinical situation and to compare the data with previous results obtained with the drug. This report is an updated analysis: the first 30 patients form the basis of a previous report (5).

Patients and Methods

Sixty-five women with advanced breast cancer were treated with aminoglutethimide at a single center between September 1978 and July 1981. The following criteria were fulfilled by all patients prior to treatment: objective evidence of metastases from histologically confirmed breast carcinoma; an Eastern Cooperative Oncology Group performance status of 3 or better; resistance to or disease progression following an initial response to prior endocrine therapy; resistance to, unsuitability for, or disease progression following an initial response to combination chemotherapy.

Aminoglutethimide was given at an initial dose of 250 mg twice a day p.o. together with cortisone acetate, 25 mg twice a day. All patients also routinely received fludrocortisone, 0.1 mg daily. Seven days later, if this treatment was well tolerated, aminoglutethimide dosage was increased to 250 mg four times a day and remained at that level thereafter. Prior to therapy, patient assessment included clinical examination, peripheral blood count, serum biochemistry, chest X-ray, and isotope bone and liver scans. Assessment was repeated at 4- to 6-weekly intervals, and scan investigations along with radiological skeletal surveys or bone marrow aspirates were repeated if metastases were suspected according to physical findings, symptoms, or laboratory results. The minimum duration of treatment before assessment was performed was 4 weeks. Responding patients continued aminoglutethimide treatment until there was evidence of disease progression. Of the 65 patients treated with aminoglutethimide, 13 are not evaluable for response. These include 6 patients who died within 4 weeks of starting aminoglutethimide and 6 patients in whom aminoglutethimide treatment was discontinued within 4 weeks because of intolerable side effects, chiefly drowsiness. One additional patient was not evaluable because of protocol violation (simultaneous chemotherapy given in error). Fifty-two patients were therefore evaluable for response assessment, and this was carried out according to standard UICC criteria (4). Their mean age was 58 years (range, 35 to 85 years), and all patients were postmenopausal or had undergone surgical oophorectomy or radiation menopause. Thirty-eight patients had undergone prior radiotherapy, and 40 of the 52 evaluable patients had received prior chemotherapy using 2 or 3 drug combinations, which included Adriamycin, cyclophosphamide, methotrexate, 5-fluorouracil, or vincristine. All patients had received prior endocrine therapy which in all but 3 cases had included tamoxifen. In 6 patients, prior endocrine therapy also included estrogen or androgens; while in 7 patients, prior endocrine therapy included either oophorectomy or radiation menopause. In the majority of cases, i.e., in 37 of 52 evaluable patients, samples of primary breast tumor were not obtained for assay of estrogen receptor levels.

Results

Fifty-two patients were evaluable for response, and of these
Aminoglutethimide treatment of 52 patients with advanced breast cancer: analysis of response by disease site

<table>
<thead>
<tr>
<th>Site</th>
<th>No. of patients</th>
<th>No. of responses</th>
<th>Response rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soft tissue</td>
<td>34</td>
<td>10</td>
<td>29</td>
</tr>
<tr>
<td>Bone</td>
<td>30</td>
<td>6*</td>
<td>0</td>
</tr>
<tr>
<td>Liver</td>
<td>19</td>
<td>2*</td>
<td>11</td>
</tr>
<tr>
<td>Lung</td>
<td>15</td>
<td>3</td>
<td>20</td>
</tr>
</tbody>
</table>

* Nine patients experienced marked relief of bone pain without objective evidence of response.

Further analyses were carried out in order to establish any other predictive factors for a response to aminoglutethimide. There was no difference in mean age between aminoglutethimide responders and non-responders (χ² = 6.95).

Response according to site of disease for the whole series is shown in Table 2. The highest response rate (29%) was seen for soft tissue disease, while none of the 30 patients with bone metastases demonstrated an objective response at that site.

Of the 52 evaluable patients, 49 had received prior tamoxifen, and details of response are recorded in Table 3. In 8 cases, a response to prior tamoxifen could not be determined because of lack of measurable disease. Of the remaining 41 patients, 10 (24%) showed a partial response to prior tamoxifen, and of these 4 (10%) responded to subsequent aminoglutethimide. Twenty patients (49%) progressed on prior tamoxifen, and of these 2 (10%) responded to subsequent aminoglutethimide.

Forty of the 52 evaluable patients received prior chemotherapy to which 24 (60%) had responded. Seven (29%) of these 24 responding patients also responded to subsequent aminoglutethimide therapy, while no patient progressing on prior chemotherapy responded to subsequent aminoglutethimide. Of the 12 patients who did not receive prior chemotherapy in this series, 3 (25%) responded to the subsequent aminoglutethimide therapy.

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thimide responders (58 years) and nonresponders (55 years). Similarly, no significant difference in disease-free interval between mastectomy and first relapse was apparent between responders to aminoglutethimide (disease-free interval of 30 months) and nonresponders (interval of 33 months). Estrogen receptor data were available in only 15 cases and were insufficient for any conclusions to be drawn. The only pretreatment variable which differed significantly between aminoglutethimide responders and nonresponders was the Eastern Cooperative Oncology Group performance status; for responders the mean performance status was 1.7 (p < 0.02).

With respect to side effects, the total incidence in 58 patients evaluable for toxicity was 36%, and these are illustrated in Table 4. In 6 cases (10%), side effects, chiefly drowsiness, were severe enough to cause treatment to be discontinued. In the remaining 15 cases, the side effects were mild and generally resolved spontaneously with continued treatment.

**Discussion**

The results reported here differ in 2 major respects from previously published studies of aminoglutethimide in advanced breast cancer. The overall response rate (19%), with a further 23% showing stable disease, is lower, and the response durations are shorter than previously recorded; and it seems probable that these differences are due to the extensive prior treatment for metastatic disease which was given to the patients in this series. Despite these differences, however, certain common features can be seen. These include the frequency of soft tissue response relative to response in other sites, the observation that symptomatic but not objective response in bone metastases is sometimes seen, and the relatively low incidence of significant side effects. In addition, a response to endocrine therapy, i.e., tamoxifen, is confirmed as indicating an increased likelihood of a response to subsequent aminoglutethimide, although, as in previous studies, patients showing resistance to prior tamoxifen did occasionally respond to aminoglutethimide (7, 11) (in 10% of cases in this series).

Most previous reports of aminoglutethimide include either patients with metastatic breast cancer for which the drug represented the first form of treatment for metastases or patients who had not been extensively pretreated with chemotherapy. In those circumstances, response rates of approximately 35% with durations of response in excess of 12 months could be expected. It has previously been noted that in general a shorter duration of response to secondary therapy is often the case when patients with breast cancer are treated sequentially (1). This observation is confirmed by the results in this series, and the data would support the view that, for optimum results with aminoglutethimide, the drug should be used early in the therapeutic sequence.

It is of some interest, however, to note that, with respect to overall survival from the date of first relapse, the median survivals in this series both for aminoglutethimide responders (48 months) and nonresponders (28 months) are very similar to those recorded in previous series for patients treated with aminoglutethimide when the drug was used much earlier in the therapeutic sequence (8). These data would suggest that, for patients receiving sequential endocrine therapy and chemotherapy for advanced breast cancer, the order in which different modalities are given is unlikely to influence overall survival. Thus, with certain exceptions where life-threatening metastases may exist, primary considerations regarding treatment sequence should be related to patient acceptability.

**Acknowledgments**

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**References**

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