Comparison of Surgical Adrenalectomy to Medical Adrenalectomy in Patients with Metastatic Carcinoma of the Breast

Samuel A. Wells, Jr., Thomas J. Worgul, Eugeniusz Samojlik, Alice E. Boucher, Allan Lipton, Harold Harvey, Deborah White, Emma Smart, Charles Cox, and Richard J. Santen

Department of Surgery, Duke University Medical Center, Durham, North Carolina 27710, and the Divisions of Endocrinology and Oncology, Department of Medicine, and the Specialized Cancer Research Center, The Milton S. Hershey Medical Center, Pennsylvania State University, Hershey, Pennsylvania 17033

Abstract

Surgical adrenalectomy has been an accepted endocrine-ablative procedure that is often used in postmenopausal patients with metastatic carcinoma of the breast. The operation, however, has a fixed mortality and an appreciable morbidity. Adrenalectomy also increases the susceptibility of the patient to the stress of subsequent disease progression and its treatment with chemotherapy and X-ray therapy. Because of these disadvantages, various nonsurgical methods of altering the hormonal milieu in patients with metastatic breast carcinoma have been sought. The present study compared a form of 'medical adrenalectomy' with surgical adrenalectomy in a randomized, controlled trial.

Ninety-six postmenopausal women with metastatic carcinoma of the breast were randomized to receive either surgical adrenalectomy (n = 46) or medical therapy p.o. (n = 50) with an adrenal inhibitor, aminoglutethimide (AG) (1000 mg/day) plus replacement hydrocortisone (HC) (40 mg/day). Forty medical patients and 29 surgical patients remained evaluable after inclusion into the study. None of the pretreatment variables (patient age, months after menopause, disease-free interval, or site of involvement) differed significantly between the groups of evaluable patients. Fifty-three percent of patients treated with AG plus HC had objective responses compared to 45% of patients treated by surgical adrenalectomy (p, not significant).

An additional 5% in the surgical adrenalectomy category experienced disease stabilization. Regressions lasted 17.2 ± 1.7 (S.E.) months in the medical group and 17.1 ± 2.2 in the surgical group (p, not significant). Median survival after objective response to AG plus HC (45 months) did not differ significantly from that following surgery (36 months).

The statistical approach to analysis of this study posed a single question: Is surgical adrenalectomy superior to medical adrenalectomy? It was reasoned that AG plus HC would be preferred to surgical adrenalectomy on practical grounds if the operative method was not proved superior. The null hypothesis designed to answer this question was rejected with statistical significance of \( p = 0.01 \) and \( p = 0.07 \) for differences of 20 and 10%, respectively. Therefore, the chance that surgical adrenalectomy is 20% superior to adrenalectomy is less than 1%. These data provide strong evidence that AG plus HC produces clinical remissions of breast carcinoma as frequently and for the same duration as does surgical adrenalectomy.

Introduction

For years, hormonal therapy has played an important role in the management of patients with metastatic carcinoma of the breast. In actively menstruating females, recurrent breast carcinoma has most often been treated by ovariectomy, whereas in postmenopausal patients, it has been managed by either additive therapy (estrogen, androgen, or progestin) or ablative therapy (adrenalectomy, hypophysectomy, or high-dose glucocorticoids administered to suppress pituitary adrenocorticotropic hormone and thereby inhibit adrenal cortical secretion). The specific hormonal therapy chosen, i.e., additive or ablative, depended primarily on the preference of the responsible clinician. With the development of methods (5) to quantitate estrogen receptor protein in breast carcinoma cells, it became possible to predict with greater certainty which patients were or were not likely to respond to hormonal therapy. Approximately 50% of patients with breast carcinoma cells that contained increased concentrations of estrogen receptor responded to hormonal therapy, whereas less than 5% of patients with breast carcinomas that contained measurable quantities of estrogen receptor responded to hormonal therapy. Subsequently, the ability to quantitate progesterone receptor protein further improved the ability of the clinician to predict response to hormonal therapy (3).

The use of surgical ablative procedures in postmenopausal patients with metastatic breast carcinoma was associated with significant disadvantages. Not only was there a significant morbidity and a fixed mortality associated with the operations, but there was a permanent postoperative dependence on glucocorticoid and mineralocorticoid replacement therapy. Since surgical adrenalectomy was at best palliative, patients would at some point develop disease recurrence and be subjected to other therapy, most commonly chemotherapy. Because of the stress associated with disease progression and the side effects (particularly gastrointestinal) of therapy, the dose of steroids often had to be increased, and in severe cases the drugs had to be administered i.v. Because of these difficulties, alternatives to surgical adrenalectomy were sought.

In 1973, Griffiths et al. (2) demonstrated that the administration of 1 to 2.5 g of AG and 0.75 mg of dexamethasone daily resulted in disease remission in 3 of 9 patients with metastatic carcinoma of the breast. Even though the remissions lasted for 2, 7, and 9 months in the 3 responders, there was only transient inhibition of urinary adrenal steroid excretion. It was shown subsequently by Santen et al. (11) and Lipton et al. (6) that AG increased the metabolic degradation of dexamethasone, thereby reducing its bioavailability. With the administration of AG, aminoglutethimide; HC, hydrocortisone; NS, not significant.

1 Presented at the Conference "Aromatase: New Perspectives for Breast Cancer," December 6 to 9, 1981, Key Biscayne, Fla. Supported in part by Contract NCI-CB-53851 from the NIH, a Grant 1P30 CA 18450 from the Department of Health and Human Services, and Grant RR 30 from the Division of Research Resources, NIH.

2 To whom requests for reprints should be addressed, at Department of Surgery, Washington University School of Medicine, 4960 Audubon Ave., St. Louis, Mo. 63110
higher doses of dexamethasone in the range of 1.5 to 3.0 mg a day, it was possible to suppress markedly adrenal cortical secretion. When it was subsequently demonstrated (13) that there was no drug interaction between AG and HC, this drug combination became the medical adrenalectomy regimen of choice. In a clinical trial of 50 patients with metastatic breast carcinoma, the administration of AG and glucocorticoid induced disease remission in approximately 40% of patients (17). Similar results were obtained by Smith et al. (16).

To determine the comparability of AG and HC to surgical adrenalectomy, 96 postmenopausal women with metastatic breast carcinoma were randomized to receive one or the other of these therapies.

Materials and Methods

Patient Entry. Postmenopausal or surgically ovariectomized patients with inoperable or metastatic carcinoma of the breast were studied at either the Milton S. Hershey Medical Center of Pennsylvania State University or the Duke University Medical Center. The metastatic lesions were bidimensionally measurable and localized to the skin, soft tissue, bone, lung, or viscera. Patients also had a projected life expectancy of more than 3 months and an Eastern Cooperative Oncology Group performance score of 3 or better (4). Patients were entered if estrogen receptor levels exceeded 3 fmol/mg of cytosol protein in primary or metastatic tissue. Patients were also entered if estrogen receptor data were not available, i.e., unknown estrogen receptor status. Patients were excluded from entry if 80 years of age or older, if greater than one-third of the liver was involved, if there was central nervous system involvement, if there was a life expectancy of less than 3 months, if estrogen receptor levels were less than 3 fmol/mg of cytosol protein, or if chemotherapy or hormonal therapy were administered within 1 month before entry.

Stratification and Randomization. A modification of the method of Zelen (18) was used to randomize patients before obtaining informed consent. Stratification parameters were estrogen receptor status, disease-free interval (more or less than 2 years), and site of dominant disease (skin, soft tissue, bone, or viscera). A card representing the appropriate stratification category, i.e., "medical" or "surgical," was then pulled. After randomization, the study was explained to the patients, and the potential risk and benefits of the procedure as well as other therapeutic options available were discussed. Written, informed consent was obtained.

Response Criteria. Responses were determined with the criteria utilized in other internally reviewed breast cancer trials (4). Responses in each case were reviewed by 2 outside reviewers sponsored by the National Cancer Institute, NIH.

Staging Procedures. Prior to patient entry and at 3-month intervals following initiation of treatment, the patients were examined and evaluated with complete blood count, chest X-ray, bone scan, skeletal survey, liver scan, and liver function tests. All lesions were photographed and measured. Although response was judged by responsible clinicians, the final assessment of response was determined by the outside reviewers.

Therapy

Surgical Adrenalectomy. In the majority of patients, the adrenal glands were removed by a posterior approach; in other patients, a transabdominal incision was used. Postoperatively, replacement steroid therapy consisted of 40 mg (in divided doses) of HC per day and fludrocortisone acetate, 0.1 mg, twice per week.

Medical Adrenalectomy. The initial dose of AG was 250 mg twice daily. On the 15th day of therapy, this dose was increased to 250 mg 4 times per day. HC was administered initially in a dose of 100 mg/day in divided doses; on the 15th day, the dose was decreased to 40 mg/day. This therapy was continued until there was evidence of disease progression.

Statistical Analysis. Differences in certain clinical variables were determined by χ² analysis. To evaluate statistical differences in the life table analysis, the methods of Mantel (7) and Breslow (1) were used. A null hypothesis was designed to test whether surgical adrenalectomy produced objective tumor regression 20 or 10% more frequently than did medical adrenalectomy.

Results

Ninety-six patients entered the study. Forty of 50 patients who entered the medical arm and 29 of 46 patients who entered the surgical arm remained evaluable after inclusion into the study. Ten medical patients were inevaluable because of either drug toxicity, premature cessation of drugs, or insufficient clinical data for external review. Seventeen surgical patients were inevaluable for review because of either insufficient data, rapid progression of disease precluding surgery, or refusal of surgery, after randomization.

Of the pretreatment variables (age, months after menopause, disease-free interval, site of involvement, and percentage with positive or unknown estrogen receptor status), none differed significantly between the 2 groups.

Response to Therapy. Of 40 women treated by the AG and HC regimen, 21 (53%) had either a partial (19 women) or complete (2 women) regression. Of 29 patients treated by surgical adrenalectomy, 13 patients (45%) experienced partial regressions. Additionally, 2 patients (7%) had stabilization of bone lesions and pain relief for 6 months. Statistically, there was no significant difference in the responses between the 2 groups. In Chart 1 are shown responses according to the site of disease and estrogen receptor status. When the 2 treatments were compared, there was no significant difference at any disease site nor was there a significant difference in the response to therapy, considering only patients with known estrogen receptor positivity or unknown estrogen receptor status.

Chart 1. Responses of patients to AG plus HC or surgical adrenalectomy.

Open bars, AG plus HC; solid bars, surgical adrenalectomy. ER, estrogen receptor; CR, complete regression; PR, partial regression; S, stable disease; N, number of patients in respective groups. Reproduced with permission from the New England Journal of Medicine (15).
gen receptor-positive breast carcinomas.

In Chart 2 is shown a life table analysis of the duration of response between the medical and surgical adrenalectomy groups. There was no significant difference in the duration of response between the surgical adrenalectomy and the medical adrenalectomy groups. Mean response duration for the AG-HC group was 17.2 ± 1.7 months and 17.1 ± 2.2 months for the surgically treated patients (p, NS). As shown in Chart 3, median survival following response to either form of therapy also did not differ between groups (surgical, 36 months; medical, 45 months) (p, NS). Patients who progressed while on AG-HC had a median survival of 13 versus 21 months for the surgical group (p, NS life table analysis not shown).

Four of 29 patients with surgical adrenalectomy developed disease recurrence and were treated with AG and HC. Two of the 4 patients responded.

Concomitant with the clinical studies, several parameters of adrenal cortical function and steroid secretion were evaluated.

The results of these studies are presented in a separate paper in this supplement (10, 12).

Complications of Therapy. It is known that patients receiving AG develop transient complications in the first 4 to 6 weeks of treatment (17). Side effects were noted in our patients and included lethargy (48%), skin rash (33%), dizziness (20%), and instability of gait (10%). The complications were transient, and almost all disappeared after the sixth week of treatment. Of patients receiving AG and HC, the therapy was terminated in 4 patients because of severe lethargy and in one patient because of transient pancytopenia.

In patients undergoing surgical adrenalectomy, one patient developed a postoperative empyema and subsequently a lung abscess. An episode of acute adrenal insufficiency was noticed in 5 (16%) of 29 patients in the surgical group.

Statistical Analysis. The hypothesis that the rate of response to surgical adrenalectomy was 20% greater than that achieved with medical adrenalectomy was rejected with a p value of less than 0.01. The hypothesis that the rate of response was 10% greater with surgery was rejected with a p value equal to 0.07. In addition, survival after an initial response to surgical adrenalectomy was not longer than that observed after medical adrenalectomy. It can be concluded, therefore, that surgical adrenalectomy was not superior to medical adrenalectomy in our patients.

Discussion

Even though surgical adrenalectomy and hypophysectomy have proven effective in the management of patients with metastatic carcinoma of the breast, both operations are associated with an appreciable morbidity and a low but significant mortality. Even the administration of hormone-additive therapies (i.e., estrogens or androgens) is associated with appreciable side effects, which have limited their use to highly selected patients.

In the present study, it has been shown that the combined regimen of AG and HC offers distinct advantages over surgical adrenalectomy in the treatment of patients with recurrent breast carcinoma. A comparison of the 2 therapies revealed no statistically significant differences in the incidence of disease remission or in the length of remission and patient survival. Upon termination of AG and HC, adrenal function returns to normal within 3 or 4 days, whereas after surgical adrenalectomy, the patient is dependent on steroid replacement for life. Subsequent chemotherapy or X-ray therapy is tolerated less well by the postadrenalectomy patient than by the intact patient. Furthermore, the medical adrenalectomy regimen is much less expensive and does not require hospitalization. The adverse reactions (lethargy, skin rash, and instability of gait) associated with AG administration occur early during drug administration, are transient, and are rarely a limiting factor in chronic drug administration.

As shown elsewhere in this supplement (12), the degree of suppression of adrenal cortical secretion is similar when comparing patients undergoing medical or surgical adrenalectomy. Additional pharmacological actions of AG, including inhibition of the conversion of androgens to estrogens (aromatization), in peripheral tissues and a sparing effect of Δ4-androgen (androstenedione, testosterone, and dihydrotestosterone) secretion are of added benefit to the patient with breast carcinoma.
AG appears also to be useful in patients who have had prior hormonal therapy. Even though regressions occur more frequently in prior endocrine responders (14), many women who have failed hormonal therapy will respond subsequently to AG. In the present study, 2 patients responded to AG and HC after an initial response to surgical adrenalectomy was followed by disease progression. No patients in our study were subjected to surgical adrenalectomy after AG therapy. However, Newsome et al. (9) treated 19 patients with metastatic breast carcinoma with AG for 3 months and then subjected them to adrenalectomy. Patients who failed to respond to AG failed to respond to subsequent adrenalectomy.

It appears clear that AG is preferred to surgical adrenalectomy in the management of postmenopausal patients with recurrent breast carcinoma. A more timely question is whether in these patients AG is superior to antiestrogen therapy and, in particular, tamoxifen. Clinical trials comparing these 2 therapeutic modalities have been completed, and the results are presented elsewhere in this supplement (6).

References
Comparison of Surgical Adrenalectomy to Medical Adrenalectomy in Patients with Metastatic Carcinoma of the Breast

Samuel A. Wells, Jr., Thomas J. Worgul, Eugeniusz Samojlik, et al.

Cancer Res 1982;42:3454s-3457s.

Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/42/8_Supplement/3454s

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.