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Phase II study of flutamide in patients with metastatic breast cancer. A National Cancer Institute of Canada Clinical Trials Group study

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Summary

The National Cancer Institute of Canada (NCIC) Clinical Trials Group conducted a phase II study of the oral antiandrogen flutamide in 33 patients with metastatic breast cancer. Eight patients had received no prior systemic therapy for their metastatic disease and 13 had only one site of metastasis. Toxicity occurred in 18 of the 33 patients and was primarily gastrointestinal. It ranged in severity from mild to severe with 4 patients discontinuing treatment early because of nausea, vomiting, diarrhea or stomatitis. One response, of 8 weeks duration, was noted in 29 evaluable patients. We conclude that flutamide does not have meaningful antitumour activity in breast cancer and plan no further trials of the drug in this disease.

Introduction

A variety of hormonal therapies have been used to control metastatic carcinoma of the breast including ovarian ablation, hypophysectomy, diethylstilboestrol, testosterone, tamoxifen, megestrol acetate and aminoglutethimide [1]. The probability that a patient will respond to one or more of these agents is 50 to 70% provided that the estrogen receptor status of their tumor is positive. The response rate of a patient with a negative estrogen receptor status is 5 to 11% [2,3].

Androgen receptor activity can be measured in 30–40% of human breast cancers and its presence does not necessarily parallel estrogen or progesterone receptor positivity [4–6]. Dihydroepiandrostenedione (DHEA) of adrenal origin may play a role in the growth of breast carcinoma [7], and the androgen receptor is thought to be involved in progestin-induced regressions of metastatic breast cancer [5,8].

For these reasons, the NCIC Clinical Trials Group undertook a phase II study of the antiandrogen flutamide in patients with metastatic breast carcinoma. Flutamide, a non-steroidal substituted anilide, is devoid of any other hormonal properties, and has been efficacious and well tolerated in men with metastatic carcinoma of the prostate. Its primary toxicities in these studies were gynecomastia and/or nipple tenderness. Less frequently seen were nausea, vomiting, fatigue and insomnia. There is no data on its use in women or its efficacy in breast carcinoma. The dose selected for this study was that which was known to be tolerable and effective in prostatic cancer [9].

Materials and methods

Between March 1985 and March 1986, 35 patients were entered onto this phase II study. Eligibility criteria included: histologic proof of breast cancer;

documented measurable metastatic disease; Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2; ≤ 2 prior chemotherapy regimens and/or ≤ 2 *failed* hormonal therapies for metastatic disease; documented estrogen receptor status (both estrogen (ER) and progesterone (PR) receptor positive and negative patients were eligible); baseline granulocyte count > 1.0×10^9/L, platelet count ≥ 75×10^9/L, bilirubin ≤ 1.5 × normal, creatinine ≤ twice normal, and written informed consent. Patients who were estrogen receptor positive were encouraged to have had a trial of tamoxifen before entry in the study. It was recommended, but not required, that flutamide be given as the second hormonal treatment after tamoxifen in ER positive patients, and as the first hormonal therapy in ER negative patients. Patients who had been receiving hormone therapy immediately before starting flutamide had to have stopped this treatment for at least 4 weeks in order not to confuse a withdrawal response with a therapeutic effect of flutamide.

Androgen receptor status was not available on any of the patients' tumours. Flutamide was supplied by Schering Canada Incorporated. The drug was administered orally in a dose of 250 mg three times daily. Therapy was given for a minimum of 8 weeks unless rapid progression was evident, or unacceptable toxicity was documented during that time. The dose of flutamide was decreased to 250 mg twice daily for severe nausea and vomiting.

Patients were followed every 4 weeks by history, physical examination, clinical tumour measurement and radiographic measurement of index lesions. Hematology and biochemistry were done week 1, 4 and every 4 weeks thereafter. Response criteria were as follows: complete response (CR): Complete disappearance of all disease for a minimum of at least 4 weeks duration. Partial response (PR): 50% or greater decrease in the sum of the products of the diameters of measurable lesions for a minimum of 4 weeks duration. Stable disease (SD): disease regression < 50% or increase of < 25% for a minimum duration of 8 weeks; Progressive disease (PD): > 25% increase in the size of measured lesions or appearance of any new lesions. Response duration was measured from the time measurement criteria were first met until relapse or progression.

Table 1. Patient characteristics (n = 33)

Median age in years (range)	56 (36–72)
Performance status (ECOG)	# patients
0	12
1	17
2	4
ER status	
Positive	16
Negative	17
Prior systemic therapy	
None	8
ER positive patients (n = 16)	
0 hormone	3
1 hormone	3
≥2 hormones	10
0 chemotherapy	10
1 combination chemotherapy	3
2 combination chemotherapy	3
ER negative patients (n = 17)	
0 hormone	11
1 hormone	5
2 hormones	1
0 chemotherapy	8
1 combination chemotherapy	5
2 combination chemotherapy	4

Results

Thirty-five patients were entered on this phase II study. Of these, 2 were ineligible (estrogen receptor unknown-1 patient, no measurable disease-1 patient). All 33 eligible patients were evaluable for toxicity, but only 29 could be evaluated for response. Four patients discontinued treatment early because of toxicity as outlined below.

The characteristics of the 33 eligible patients are outlined in Table 1. Twenty-nine were ECOG performance status 0 or 1, and 16 were estrogen receptor positive. Eight patients had had no prior therapy of any type for systemic disease. Of the estrogen receptor positive group (16 patients), 13 had received one or more hormone treatments, but 10 had received no chemotherapy. In the estrogen receptor negative group (17 patients) 11 had re-

Table 2. Sites of disease

Site	No patients
Soft tissue	25
Bone	11
Liver	3
Lung	13
CNS	3
No patients with only one site metastases:	13

Table 3. Toxicity of flutamide*
Worst ever by patient (n = 33 evaluable)

	Grade			
	1	2	3	Total
Nausea/vomiting	4	3	1	8
Stomatitis	4	2		6
Diarrhea	1	3		4
Anorexia	2			2
No toxicity				15

*Toxicity was graded using U.S. National Cancer Institute Standard Criteria

ceived no hormone therapy, and 8 no chemotherapy.

The sites of disease in the patients studied are shown in Table 2. Thirteen of the 33 patients had only one site of involvement and the majority of patients had disease involving soft tissue, bone and/or lung. Only 3 patients had liver involvement and an additional 3 had CNS involvement.

The median duration of flutamide therapy was 7 weeks (range 1–33). Twenty received less than 8 weeks of treatment: 16 because of progressive disease and the other 4 because of gastrointestinal toxicity (detailed below). These latter patients received only one to two weeks of treatment and were thus considered inevaluable for response. The toxicities produced by flutamide are shown in Table 3 and consisted primarily of gastrointestinal symptoms such as nausea and vomiting, stomatitis, diarrhea and anorexia. No hematologic toxicity was seen. Three patients showed a transient asymptomatic increase in asparate aminotransferase (AST) up to 3 times baseline which was felt to be drug related. In one patient the AST fell to normal while on flutamide and in the other two the AST normalized after the drug was discontinued for other reasons. It should be noted that approximately half the patients on the trial experienced no toxic effects.

Only one partial response of 8 weeks' duration was observed. It occurred in a 54 year-old patient with a biopsy proven ER and PR negative infraclavicular mass. Her only prior therapy had been combination chemotherapy with 5-FU, adriamycin and cyclophosphamide. Five patients in total had stable disease ranging in duration from 8 to 36 weeks. The remaining 23 patients all progressed on therapy.

Discussion

We observed only one response in 29 patients with breast cancer given 750 mg of oral flutamide daily. This observation excludes an overall true response rate of >15% with 95% confidence. The selected dose of flutamide was equivalent to that used in men with prostatic carcinoma, and while it could be argued that a different dose or schedule could have produced better results, no data exist to help guide such a strategy in this disease. Toxicities seen in this group of women are similar to those seen in men when given flutamide with the exception that breast tenderness was not documented.

Unfortunately, tumour samples for androgen receptors were not obtained as part of this trial. Measurements of such receptors should be considered in planning future phase II studies of androgen or anti-androgen therapy in breast cancer patients as it is possible that subsets of patients which have a higher probability of response to these agents may be identified by these means. Because occasional patients experienced significant toxicity from flutamide and the drug did not produce meaningful antitumour activity in breast cancer, we plan no future studies of flutamide as a single agent, or in combination, in patients with this disease.

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