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Phase II Study of the Antifolate N^{10}-Propargyl-5,8-dideazafolic Acid (CB 3717) in Advanced Breast Cancer

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Abstract—*Fifty-two patients with progressive advanced breast cancer were treated with the novel antifolate CB* 3717 (N^{10}-*propargyl-5,8-dideazofolic acid) which inhibits thymidylate synthetase. Forty-six patients were pretreated with hormones,* 43 *with cytotoxic chemotherapy and* 39 *patients with both treatments. Eight of* 48 *patients* (16.6%) *evaluable for response had partial responses (confidence limits* 7.4–30.2%, 95% *confidence level) following CB* 3717 *administration. Liver function abnormalities, reversible in most cases, were the commonest toxicities and were frequently accompanied by malaise. Severe renal failure occurred in eight patients, five of whom had had partial responses to CB* 3717. *This study shows the importance of thymidylate synthetase as a target for therapy but the clinical value of CB* 3717 *is limited by its hepatic and renal toxicities.*

INTRODUCTION

THE QUINAZOLINE FOLATE analogue N^{10}-propargyl-5,8-didaezafolic acid [*N*-(4-(-((2-amino-4-hydroxy-6-quinazolinyl)methyl)prop-2-ynylamino)benzoyl)-L-glutamic acid; CB3717] is a tight binding inhibitor of thymidylate synthetase and in human tumour cell lines overcame methotrexate (MTX) resistance, regardless of whether the resistance was due to an elevated level of dihydrofolate reductase or reduced membrane transport of MTX [1, 2]. In phase I evaluation, dose limiting toxicity was renal; responses occurred at doses from 200 to 600 mg/m^2 and most patients developed reversible biochemical abnormalities of liver function associated with malaise [3]. Myelotoxicity was infrequent and was not dose-related [3]. Three partial responses were observed following CB3717 administration in eight heavily pre-treated breast cancer patients in phase I study. One of the responding patients was resistant to a previous methotrexate-containing chemotherapy combination [3]. We therefore gave CB3717 to 52 patients with assessable locally advanced and/or metastatic breast cancer in a phase II study.

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CB 3717 was supplied by Imperial Chemical Industries (ICI) Pharmaceutical Division, Mereside, Alderley Park, Macclesfield, Cheshire, U.K.

PATIENTS AND METHODS

Patient characteristics are shown in Table 1. Most patients were heavily pre-treated before CB 3717; only one patient had no prior systemic therapy. World Health Organization (WHO) criteria were applied to response assessments and graded toxic effects [4]. Fifteen patients were given oral prednisolone, usually 20–30 mg daily for 7 days after some CB 3717 courses, as steroids have ameliorated CB 3717 induced malaise [3]. Three other patients were given continuous oral steroids during CB 3717 therapy for associated complications, i.e. malignant hypercalcaemia, lymphangitis and a case of presumed hypoadrenalinism. CB 3717 was infused intravenously over 1 h every 3 weeks. Renal function was determined by 24 h creatinine or EDTA clearances at initiation of CB 3717 and serum hepatic and renal biochemistry

and full blood counts were generally estimated weekly and always before each course of CB 3717. Planned starting doses of CB 3717 were 400 mg/m^2, subject to reduction to 300 mg/m^2 if pre-therapy 24 h EDTA or creatinine clearances were < 60 ml/min and/or serum alkaline phosphatase levels were elevated.

*Table 1. Characteristics in 52 patients**

Median age in years (range)	55 (33–75)
Premenopausal patients	12
Postmenopausal patients	40
Prior treatment	
Hormone therapy	46
Chemotherapy	43
Methotrexate in combination	25
Median No. of prior therapy regimens (range)	
Hormone therapies	2 (1–3)
Chemotherapies	2 (1–3)
No. of CB 3717 doses†	
400 mg/m^2 every 3 weeks	67
300 mg/m^2 every 3 weeks	61
200 mg/m^2 every 3 weeks	6
100 mg/m^2 every 3 weeks	3
Total No. of courses	137
Median (range)	2 (1–7)

*Unless otherwise stated values = No. of patients.
†Because of reduced renal EDTA or creatinine clearance rates before CB 3717, starting doses were 300 mg/m^2 in 19 patients and 200 mg/m^2 in two patients. Some courses were escalated to a maximum of 400 mg/m^2 or reduced to a minimum of 100 mg/m^2 depending on symptomatic/biochemical toxicity.

RESULTS

Of 52 patients entered into study, 48 were considered evaluable for response, four patients having died within 21 days after the first CB3717 infusion. Eight patients had partial responses. Thus the response rate was 16.6% (confidence limits 7.4–30.2%; 95% confidence level). Details of responding patients are shown in Table 2. In addition two other heavily pre-treated patients had less than 50% shrinkage in pulmonary and skin metastases for 17 and 20 weeks respectively and a third patient, also heavily pretreated, had shrinkage of a pleural effusion and increasing sclerosis in lytic bone metastases (considered to represent response to CB 3717). Two patients with partial and two with minor responses had steroids with CB 3717 and although the addition of steroids could cause difficulty in response evaluation, steroids were not given until after responses to CB 1717 were assessed in all but one case. Furthermore all responding patients had progressed despite prior hormone therapy, making the likelihood of a steroid contribution to response remote.

Toxicity is summarized in Table 3. Four patients died within 3 weeks after first CB 3717 course, and although unproven, treatment related deaths could not be excluded. One other patient who had liver

Table 2. Evaluation of patients with partial responses to CB 3717

Response sites	Response durations (weeks)	No. of CB 3717 courses	Prior chemotherapy and response	Major toxicity
Skin	72	6	Not given	
Skin/nodes	12	2	Response	Renal failure reversible over 16 weeks
Skin	8	1	No response (prior MTX containing regime)	Renal failure partially reversible over 8 weeks
Skin/nodes	16	5	Response	Renal failure reversible over 8 weeks
Skin/pleural	18	5	No response	Renal failure
Skin/pulmonary	12	4	No response	
Skin	13	4	Not given	
Skin	20	7	Not given	Renal failure partially reversible over 12 weeks and CB 3717 at lower dose reintroduced

CB 3717 was discontinued if renal failure was detected by rising serial serum creatinine levels (WHO grade ≥ 2) and/or by falling renal EDTA and creatinine clearances.

Table 3. Toxic effects

Toxic effects	No. of evaluable patients = 48*
Red irritant macular skin rash (generalized)	2
Radiation recall skin reactions	3
Conjunctivitis or stomatitis	9
Depression	2
Diarrhoea	1
Malaise lasting about 1 week (70 courses)	34
WHO graded toxic effects (maximum grade on any course recorded)	
Serum alkaline phosphatase	
Grade 0	13
Grade 1	23
Grade 2	6
Grade 3	5
Grade 4	1
Serum aspartate transaminase or alanine aminotransferase	
Grade 0	11
Grade 1	10
Grade 2	19
Grade 3	8
Serum bilirubin	
Grade 0	44
Grade 1	2
Grade 4	2
Nausea/vomiting	
Grade 0	19
Grade 1	14
Grade 2	9
Grade 3	6

One patient with presumed toxic death had in addition to increasing liver failure, WHO grade 4 leucocytopenia and thrombocytopenia after CB 3717.
*Four patients were not evaluable because of early deaths within 21 days after CB 3717.

metastases died with thrombocytopenia, leucopenia and increasing liver failure with ascites 23 days after her first and only infusion of CB 3717 300 mg/m^2 and these events were considered CB 3717 related. Renal toxicity resulting in a 20–50% fall from baseline in creatinine or EDTA clearances occurred in three patients, and a $> 50\%$ fall occurred in eight patients during CB 3717 therapy. Renal toxicity in responding patients (Table 2) occurring at starting CB 3717 doses of 300–400 mg/m^2 was slowly reversible on discontinuation of CB 3717. In one responding patient, CB 3717 was discontinued because of renal failure after three courses each at 400 mg/m^2. Renal failure then partially reversed over the following 3 months and CB 3717 was reintroduced at reduced doses (100 mg/m^2) for three courses without further adverse renal effects. Acute symptomatic gastrointestinal toxicity was infrequent and mild. When it occurred its onset was usually delayed for some days after CB 3717 and only six patients required therapeutic intervention for emesis.

DISCUSSION

CB 3717 is an active antimetabolite in advanced heavily pre-treated breast cancer and contrasts with the lack of activity of CB 3717 in a phase II study of minimally pre-treated mesothelioma [5].This illustrates the importance of thymidylate synthetase as a rational drug target for chemotherapy in breast cancer. The clinical usefulness of CB3717 is likely to be curtailed by its hepatic and renal toxicities. Disturbances of liver function, reversible in most cases, occurred in approximately 75% of patients and the frequently associated intermittent malaise was the most troublesome symptomatic drug toxicity. Severe renal failure occurred in eight patients, including five in partial response. Although renal toxicity was partially reversible, albeit slowly, it led to discontinuation or significant interruption of therapy in five responding patients. In the mouse accumulation of CB 3717 in the liver and kidney was considered as a likely provoking factor in the genesis of hepatic and renal toxicity [6]. If hepatic and renal toxicities could be circumvented or

ameliorated CB 3717 would be a useful non-myelosuppressive drug to treat human breast cancer. Alternatively an active analogue without significant clinical hepatic or renal toxicity might be developed.

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