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A phase II study of pemetrexed disodium (LY231514) in patients with locally recurrent or metastatic breast cancer

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Abstract

A phase II study was conducted to evaluate the activity of pemetrexed in patients with locally recurrent or metastatic breast cancer. 38 patients, median age 52 years (range 36–71 years), were given pemetrexed 600 mg/m^2 as a 10-min intravenous (i.v.) infusion every 3 weeks. Median time from diagnosis to study entry was 48 months (range 14.7–310 months). 33 of 38 patients had prior chemotherapy; 16 adjuvant, 12 metastatic and 5 in both settings. Sites of disease included skin and soft tissue (19/38) nodes (18/38), lung (17/38), liver (13/38) and bone (3/38). An overall response rate of 28% (95% confidence interval (CI): 14.2–45.2%) in 10/36 evaluable patients (1 complete response (CR), 9 partial responses (PR)), included reductions in hepatic and pulmonary metastases. 5 of 10 responders had received taxoid or anthracycline therapy for metastatic disease; 3 of these 5 had also received adjuvant chemotherapy. Median duration of response was 8 months (range 1.6–14+ months), and median survival was 13 months (95% CI 9.56–17.38 months). 167 courses were given (median five per patient; range 1–9), with 37 reductions and 33 delays. Reasons for reduction included neutropenia (11%) and mucositis (5%), with delays due to raised LFTs (21%), neutropenia (12%) and other non-treatment related events. The major haematological toxicities (Common Toxicity Criteria) (CTC) were grade 3/4 neutropenia (47%) and thrombocytopenia (15.7%) of patients. There was one report of a grade 3 infection. Non-haematological toxicities (all grades 2/3) included elevated transaminases (92%), vomiting (34%), nausea (34%) and mucositis (32%). One episode of grade 4 diarrhoea was reported. Other toxicities included a skin rash, grade 2 (42%), 3 (5%) and 4 (13%), which was ameliorated by the use of prophylactic dexamethasone. These results suggest that pemetrexed has significant antitumour activity in advanced breast cancer with responses in patients who had previously received anthracyclines and taxoids. © 2001 Elsevier Science Ltd. All rights reserved.

Keywords: Pemetrexed disodium; ALIMTA; LY231514; Metastatic breast cancer; Multitargeted antifolate; Phase II

1. Introduction

Pemetrexed disodium (ALIMTA™, LY231514, MTA), a multitargeted antifolate, differs structurally from other antifolate antimetabolites in that it has a 6-5-fused pyrrolo[2,3-d]pyrimidine nucleus instead of the usual 6-6-fused pterine or quinazoline ring system [1]. Pemetrexed is transported across cell membranes primarily by the reduced folate carrier, and once inside the cell is readily polyglutamated by folylpolyglutamate synthase [2]. This polyglutamation is believed to be responsible for a higher intracellular retention time and better inhibition of several folate-dependent enzymes than would be expected from the parent compound [3]. Pemetrexed has been shown to inhibit several folate-dependent enzymes including thymidylate synthase (TS), dihydrofolate reductase (DHFR), glycinamide ribonucleotide formyltransferase (GARFT), and aminoimidazole ribonucleotide formyltransferase (AIRCARFT). Furthermore, pemetrexed polyglutamates are more potent inhibitors of TS (80-fold) and GARFT (1500-fold) than the parent compound. Pemetrexed's spectrum of activity against folate-dependent enzymes leads to synchronisation of cells at the G_1/S interface within 12 h after treatment [4]. In the human tumour cloning assay, pemetrexed showed activity against

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tumour cells collected from patients with colorectal cancer, non-small cell lung cancer (NSCLC), renal cell carcinoma, hepatocellular carcinoma, mesothelioma and pancreatic cancer [5]. Anti-tumour activity was seen against several human tumour xenografts in nude mice including colon, pancreas, lung and mammary tumour xenografts [6].

Three dosing schedules were used in phase I testing of pemetrexed: daily×5 every 3 weeks, weekly×4 every 6 weeks and once every 3 weeks [7–9]. The main dose-limiting toxicity for all schedules was neutropenia; other reported toxicities included liver enzyme elevation, thrombocytopenia, fatigue and rash. The maximum tolerated doses for the three schedules were 4, 30, and 600 mg/m^2, respectively. Based on the toxicity profile and ease of administration, the 600 mg/m^2, once every 3 weeks schedule was chosen for phase II studies.

Pemetrexed has demonstrated clinical efficacy in multiple tumour types in the phase II setting, including metastatic colorectal cancer (response rates ranging from 17 to 20%) [10,11], pancreatic cancer (6% including one complete response) [12] and locally advanced or metastatic NSCLC, (response rates ranging from 17 to 23%) [13,14]. The toxicities in these phase II studies have been similar to observations from phase I series and included myelosuppression, mucositis, fatigue and rash. As seen in clinical studies of other antifolates, transient grade 3 and 4 elevations of liver transaminases are common but not dose-limiting. There have been no cases of persistent transaminase elevation. Myelosuppression is generally reversible, and clinically significant hepatoxicity and cutaneous toxicity was avoided through dexamethasone prophylaxis. Based on pemetrexed's broad spectrum of activity *in vitro*, in animal models, and in previous clinical trials, and its generally manageable toxicity profile, we have studied this drug in the phase II setting in patients with locally recurrent or metastatic breast cancer.

2. Patients and methods

2.1. Patient eligibility

Patients with histologically or cytologically confirmed diagnosis of breast cancer with measurable regionally recurrent or metastatic disease were entered into this phase II study. Patients could have received one chemotherapy regimen for metastatic disease, but this regimen must not have included 5-fluorouracil (5-FU) or methotrexate. Prior adjuvant therapy using regimens containing 5-FU or methotrexate was allowed as long as it was given at least 1 year prior to study entry. Patients were required to have adequate bone marrow reserve as defined by white blood cell (WBC) count $\geqslant 3.5\times10^9$/l, neutrophils $\geqslant 2.0\times10^9$/l, platelets $\geqslant 100\times10^9$/l, and haemoglobin $\geqslant 90$ g/dl. Prior radiotherapy for palliative bone metastases was allowed, but had to be to less than 30% of the bone marrow. Patients were required to have adequate hepatic function as defined by bilirubin, prothrombin time, or partial thromboplastin time $\leqslant 1.5$ times the upper limit of normal, and transaminases up to 3 times the upper limit of normal, unless liver metastases were present, in which case transaminases up to 5 times the upper limit of normal were allowed. Patients with inadequate renal function (creatinine clearance less than 0.75 ml per s) and those with significant third space accumulations (ascites and/or pleural effusions) were excluded. Patients taking vitamin supplements or those requiring allopurinol, probenecid, trimethoprim, phenytoin, cotrimoxazole or pyrimethamine were not eligible for the study. Patients taking non-steroidal anti-inflammatory drugs were required to stop them the day before, the day of, and the day following treatment; slow release preparations were stopped 5 days before treatment.

The protocol was approved by the ethical committees of the participating institutions and written informed consent was obtained from patients before treatment was initiated.

2.2. Drug administration

Pemetrexed disodium (Eli Lilly and Company), supplied as a lyophilised powder, was reconstituted with sterile normal saline, and was administered as a 10-min intravenous (i.v.) infusion at a dose of 600 mg/m^2 every 3 weeks. Full blood counts were taken weekly throughout the treatment period. Dose modifications were stipulated for myelosuppression and mucositis.

2.3. Response evaluation

Response was evaluated by standard South West Oncology Group (SWOG) criteria [15]. Duration of response was calculated as the time from first documentation of objective response to first documentation of disease progression or death due to any cause. Response was assessed by physical examination before each treatment course and by radiological measurement before every second treatment course.

2.4. Toxicity evaluation

Toxicity grading was based on the National Cancer Institute Common Toxicity Criteria (CTC). Patients were assessed weekly for haematological toxicity, including blood chemistries, and every 3–4 weeks (before each treatment course) for non-haematological toxicities.

3. Results

3.1. Patient characteristics

Thirty eight patients entered this phase II study and their characteristics are shown in Table 1. The median age of the patient group was 52 years (range 36–71). 16 patients had undergone adjuvant chemotherapy only, 5 patients had received both adjuvant chemotherapy and chemotherapy for metastatic disease, and 12 patients had received chemotherapy for metastatic disease only. The majority of patients ($n=31$) had received hormonal therapy, with patients receiving up to three lines of hormonal therapy. 32 patients received radiotherapy, most commonly in the context of breast conserving treatment for primary disease

6 patients had locally recurrent disease only, the rest having metastatic disease. The median number of sites of disease was 2 with a range of 0–5. Most patients had cutaneous and nodal disease with 25 patients having parenchymal involvement of lung and/or liver. Only 3 patients had bone metastases, a relatively low incidence for this patient population.

3.2. Toxicity

A total of 167 cycles were administered, with a median of 5 and a range of 1–9 cycles. Haematological toxicity is shown in Table 2. 18 of 38 patients experienced grade 3 or 4 neutropenia. Dose reductions as a consequence of low nadir counts were made for 4 patients and treatment was delayed for 1 patient. As a consequence of dose modifications, less than a third of chemotherapy cycles were complicated by grade 3 or 4 neutropenia and there were no episodes of neutropenic sepsis.

Non-haematological toxicities are shown in Table 2. Grade 1 alopecia was noted in 14 patients. Grade 4 skin rash occurred in 5 patients which led to dose delays and subsequent dose reductions in 2 patients. In general, the rash responded well to steroid therapy. Grade 3 diarrhoea was noted in 2 patients and grade 4 in 1 patient. Upper gastrointestinal toxicity was mild with 3 patients experiencing grade 3 nausea and 1 patient experiencing grade 3 vomiting. Grade 3 mucositis was noted in 5 patients which led to dose reductions. All patients experienced some degree of alteration of liver transaminases following treatment with pemetrexed, although these changes were asymptomatic. Although liver transaminase levels had generally returned to normal by the time the next course was due, 4 patients' treatment courses were delayed by 1 week, and 1 patient's course was delayed by 2 weeks and then reduced to allow raised transaminase levels to resolve. As a result of dose reductions and treatment delays, the received dose-intensity was 160 mg/m^2/week, 80% of the projected dose-intensity.

3.3. Response

Of the 38 patients enrolled in the study, 36 received at least two courses of pemetrexed and were therefore evaluable for response. Of the 2 patients who only received one course of treatment, 1 patient died of

Table 1
Patient characteristics ($n=38$)

Age (range) (years)	52 (36–71)
Performance status	*n* (%)
0	8 (21)
1	25 (66)
2	5 (13)
Sites of disease	
Number (median) (range)	2 (5) 1–5 (3–13)
Skin and soft tissue	19 (50)
Nodes	18 (47)
Liver	13 (34)
Lung	17 (45)
Bone	3 (8)
Prior therapy	
Surgery	38 (100)
Radiotherapy	32 (84)
Chemotherapy (adjuvant)	16 (42)
Chemotherapy (metastatic)	12 (32)
Chemotherapy (both)	5 (13)
Hormonal therapy	31 (82)
Response assessment	*n* (%)
Complete response	1 (3)
Sites of response: lung, soft tissue, lymph node	
Partial response	9 (25)
Sites of response:	
Liver	4
Lung	5
Skin and soft tissue	7
Lymph node	7
Stable disease	17 (47)

Table 2
Toxicity by treatment course

	CTC grade (% total no of courses, $n=167$)			
	1	2	3	4
Anaemia	40	23	1	0
Leucopenia	20	24	26	2
Neutropenia	20	20	20	8
Thrombocytopenia	18	4	2	2
Bilirubin	0	4	5	1
AST/ALT increases	42	30	18	0
ALK phos increases	30	9	2	0
Alopecia	22	0	0	0
Rash	13	19	2	4
Diarrhoea	10	3	1	1
Nausea	33	10	2	0
Vomiting	6	10	1	0
Stomatitis	22	13	3	0

CTC, common toxicity criteria; AST, asparate aminotransferase; ALT, alanine aminotransferase; ALK phos, alkaline phosphate.

progressive disease, and the other patient discontinued due to the physician's perception of lack of efficacy. One patient experienced complete resolution of pulmonary, cutaneous and nodal disease and a further 9 patients had partial responses for an overall response rate of 28% (95% confidence interval (CI) 14.2–45.2%). 2 partial responders had received no chemotherapy previously, and 3 patients had received adjuvant chemotherapy only, 2 with cyclophosphamide, methotrexate and 5-FU (CMF) and 1 with doxorubicin and cyclophosphamide. 3 responding patients had received chemotherapy for metastatic disease only (1 with paclitaxel and FEC (5-FU, epirubicin and cyclophosphamide), 1 with doxorubicin and ifosfamide, and 1 with gemcitabine). A further 2 responding patients had received adjuvant chemotherapy and one regimen of taxoids for metastatic disease. None of the responding patients experienced true remission from their previous treatment. 3 of the 10 responders progressed through their prior chemotherapy, and the remainder had varying periods of stable disease or non-treatment before entering the study. The median duration of response to pemetrexed was 8 months with a range of 1.6–14+ months. The median survival was 13 months (95% CI 9.56–17.38 months), as shown in Fig. 1.

4. Discussion

A large number of drugs are capable of producing responses in metastatic breast cancer, although studies which show an enhancement in survival in the metastatic setting are less common. In the past, regimens such as CMF have been widely used, and indeed a CMF regimen was one of the first adjuvant chemotherapy regimens shown to enhance survival [16]. More recently, attention has been focused on regimens containing anthracyclines and taxanes. Despite the availability of these drugs, patients still develop resistance to, and invariably die from, metastatic disease, and although relapse rates are reduced by the use of adjuvant therapy, many high-risk patients still relapse. For patients who are cured by intensive adjuvant therapy, long term side-effects such as leukaemogenesis [17] and cardiotoxicity [18], while rare, may still be of concern. As pemetrexed is an antifolate and a DHFR inhibitor, a component of its mechanism is analogous to that of methotrexate. As a TS inhibitor, pemetrexed also reproduces one of the biochemical effects of 5-FU and might therefore be expected to possess activity superior to either of these agents which are already established in breast cancer treatment.

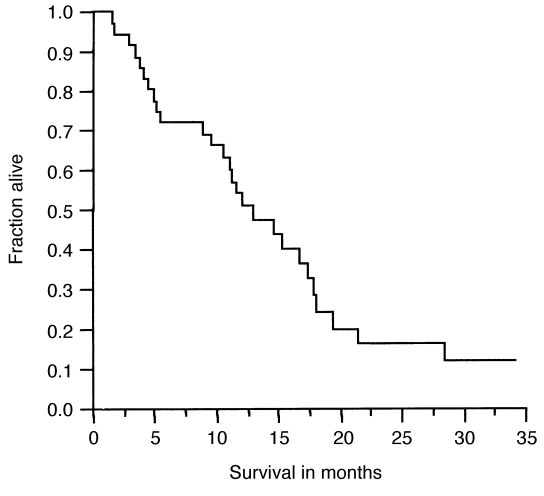

Fig. 1. Kaplan–Meier survival curve.

While pemetrexed can be shown to inhibit several folate-metabolising enzymes *in vitro*, this does not necessarily imply that these loci are important to its action. Indeed, early testing suggested that pemetrexed was functionally a TS inhibitor.

However, at higher concentrations (at approximately 0.1 μM) a purine source was required for reversal of toxicity *in vitro* [3], suggesting that the inhibition of GARFT had become significant. Clinically achieved plasma levels of pemetrexed have been clearly shown to be far higher than the levels required for multiple loci to be affected *in vitro*, ranging from approximately 200 μM shortly after treatment and remaining above 0.1 μM for up to 24 h, so alternative loci may well be affected [19]. Furthermore, biochemical evidence shows a difference in the accumulation of deoxyxadenosine triphosphate (dATP) [20] compared with the more specific TS inhibitor, raltitrexed, and resistant cell lines in which a purine source is required to protect from pemetrexed have been described [21]. These data suggest that a second biochemical target is likely to be affected following the administration of the drug to humans and may be important in circumventing drug resistance.

A number of fluoropyrimidine-based treatments of metastatic breast cancer have been evaluated in recent years. These include capecitabine, an orally available prodrug with activity in breast cancer [22]; eniluracil, a drug designed to prevent the metabolic degradation of 5-FU by dihydrothymine dehydrogenase [23], UFT [24] and infusional 5-FU [25]. These have provided useful additional therapies for patients with advanced breast cancer. Pemetrexed, on account of its different metabolism and additional distinct loci from those approached by fluoropyrimidines, may prove to be active in a non-overlapping group of patients.

Raltitrexed underwent a phase II study in patients with metastatic breast cancer who had not received chemotherapy for metastatic disease. An overall response rate of 23% on an intention to treat basis was reported, although this fell to 17% in patients who had received prior adjuvant chemotherapy and to 11% if this contained anthracyclines [26].

Pemetrexed and its polyglutamates are potent inhibitors of several folate-dependent enzymes. Increased intracellular retention time may allow more convenient schedules of administration; indeed the feasibility of a once-every-3-week schedule was confirmed in phase I studies where objective responses were noted in patients with colorectal cancer [9]. Based on these data, phase II studies have been initiated in several tumour types. The present study has demonstrated that the schedule of pemetrexed given at a dose of 600 mg/m^2 every 3 weeks is feasible in patients with metastatic breast cancer. The principal toxicities were myelosuppression, mucositis and skin rash, the latter having improved with the use of prophylactic steroids during the course of the trial. Pemetrexed was well tolerated, and the observed response rate suggests that this compound has significant single-agent activity in metastatic breast cancer. The group of patients treated were heterogeneous, however, with respect to prior chemotherapy regimens. As this study has shown promising results, further phase II trials have been initiated in Europe and the USA in specific patient populations: those previously pretreated with anthracyclines and anthracenediones, those previously pretreated with anthracyclines and taxoids, and those previously pretreated with anthracyclines, taxoids and capecitabine. In preliminary reports from Spielmann and colleagues, intriguing activity has been noted not only in patients previously pretreated with anthracycline, but also in patients who had received a taxane in the metastatic setting [27]. Further studies are planned to better define the activity of pemetrexed in locally advanced and metastatic breast cancer.

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