Phase II trial of pemetrexed disodium (ALIMTA®, LY231514) in chemotherapy-naïve patients with advanced non-small-cell lung cancer

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Received 9 July 2001; revised 2 October 2001; accepted 23 October 2001

Background: To evaluate the efficacy and safety of pemetrexed therapy for chemotherapy-naïve patients with surgically incurable non-small-cell lung cancer (NSCLC).

Patients and methods: Eligible patients received pemetrexed 600 mg/m² every 3 weeks. Restaging was performed after every two cycles of therapy and toxicity was assessed at each cycle of pemetrexed. In the absence of disease progression or undue toxicity, treatment was continued for a maximum of 12 cycles.

Results: Fifty-nine patients (median age 59 years; range 39–74 years) received a median of four cycles of pemetrexed. Nineteen patients (32%) had a ECOG performance status (PS) of two and 39 patients (66%) had stage IV disease. The most common histological sub-types were adenocarcinoma (20 patients, 34%) and large cell (18 patients, 31%). Sixteen patients (27%) had received prior radiotherapy. Nine patients achieved a partial response for an overall response rate of 15.8% (95% confidence interval CI 7% to 28%). The median duration of response was 4.9 months, and the median survival was 7.2 months. The principal toxicities were myelosuppression and rash. While grade 3 or 4 neutropenia was seen in 25 patients (42%), only two patients (3%) developed grade 3 infection. Eighteen patients (31%) developed grade 3 or 4 cutaneous toxicity, which improved with prophylactic oral dexamethasone administered for 3 days beginning the day before pemetrexed treatment. Asymptomatic elevations in hepatic biochemistry (especially alanine transaminase and aspartate transaminase) were seen in 47 patients (80%); however, these did not interfere with the dose or schedule of pemetrexed and returned to normal levels throughout the study.

Conclusions: This is the largest study confirming the encouraging single-agent activity of pemetrexed in chemotherapy-naïve patients with NSCLC. In addition, this study demonstrates that a dose of 600 mg/m² can be delivered safely; however, treatment should be restricted to patients with a PS of 0 or 1. The results of combination studies are awaited with interest.

Key words: non-small-cell lung cancer, pemetrexed, phase II

Introduction

Lung cancer remains the single most common cancer problem in the Western world. The most recent World Health Organisation data for causes of death worldwide estimated that lung cancer would be responsible for 1.2 million deaths in 2000 [1]. Seventy-five percent of cases of lung cancer are non-small-cell lung cancer (NSCLC), for which surgery remains the principal curative option. However, the curative potential of surgery is limited because the majority of patients have inoperable disease at presentation. In addition, approximately 50% of patients who undergo an operation with curative intent subsequently relapse, resulting in a large group of patients who could benefit from effective palliative therapies [2]. The treatment options in NSCLC have changed significantly in the last 5 years with the introduction of a number of new agents that appear to be more active and less toxic than older therapies (reviewed in Clarke and Boyer [3]). These compounds include the taxoids, paclitaxel and docetaxel, gemcitabine, vinorelbine and irinotecan. Reported phase II response rates for these agents as monotherapy in patients with untreated NSCLC range between 20% and 30%, with combinations producing response rates of up to 50%. However, a recent
randomised phase III study in patients with previously untreated NSCLC, performed by investigators from the Eastern Cooperative Oncology Group (ECOG), demonstrated response rates of only between 15% and 23% for combinations of a platinum derivative and each of paclitaxel, gemcitabine and docetaxel [4]. There is thus a need for new agents, especially with different mechanisms of action, to improve cure rates and palliation for patients with NSCLC.

Pemetrexed (ALIMTA®, LY231514) is a novel folate-based anticaner compound with a broad spectrum of activity against human tumour cell lines and xenograft models. Pemetrexed predominantly inhibits thymidylate synthase (TS), but is also active against other folate enzymes involved in the de novo synthesis of purines and pyrimidines, including dihydrofolate reductase (DHFR) and glycaminide ribonucleotide formyl transferase (GARFT) [5]. Like many folate-based compounds, pemetrexed is a substrate for folypolyglutamate synthetase (FPGS), and the resulting polyglutamated forms demonstrate up to 100-fold greater potency than the parent compound against TS and GARFT, but not DHFR [6]. Further evidence that pemetrexed inhibits multiple enzyme targets is demonstrated by the failure of co-administered thymidine to completely reverse pemetrexed-induced cytotoxicity in tumour cell lines. However, the combination of thymidine and a purine source, such as hypoxanthine, results in almost 100% reversal of cytotoxicity. In addition, there is evidence for incomplete cross-resistance between pemetrexed and raltitrexed (Tomudex), a specific folate-based inhibitor of TS [7].

Polyglutamation of pemetrexed also results in prolonged intracellular drug retention, thereby permitting intermittent schedules of administration. Multiple phase I schedules of pemetrexed have been evaluated, including once a week for 4 weeks re-peated every 6 weeks, once a day for 5 days repeated every 3 weeks and a single dose repeated every 3 weeks (reviewed by Rinaldi [8]). The preferred schedule was a 10-min intravenous infusion administered every 3 weeks [9]. The maximum tolerated dose (MTD) using this schedule was 700 mg/m², and the dose-limiting toxicity (DLT) was myelosuppression, although non-haematological toxicities such as rash, nausea, mucositis and fatigue were also reported. A dose of 600 mg/m² was recommended for phase II studies. The aim of this phase II trial was to investigate the activity and toxicity of pemetrexed in patients with chemotherapy-naïve, locally advanced, recurrent or metastatic NSCLC.

**Patients and methods**

**Patient selection**

All patients in this study had histologically or cytologically confirmed, bidimensionally measurable, stage III or IV NSCLC. Patients could not have received prior chemotherapy. Radiation therapy >6 weeks prior to study enrolment was allowed if the irradiated site was not the only site of measurable disease. Patients were at least 18 years of age, had an ECOG performance status (PS) ≤2 and a life expectancy of at least 12 weeks. Minimum bone marrow function requirements were white blood cell count ≥3.5 × 10⁹/l, platelets ≥100 × 10⁹/l, haemoglobin ≥9 g/dl and absolute granulocyte count (AGC) >2.0 × 10⁹/l. Minimum liver function requirements were bilirubin <1.5-fold the upper limit of normal (ULN), prothrombin time or activated partial thromboplastin time <1.5× control, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) <3-fold ULN (may be elevated to 5-fold ULN in patients with known hepatic metastases). Patients with childbearing potential were required to use adequate contraceptive precautions. Patients were ineligible if they were pregnant or breast-feeding, or had any of the following: an active infection or other serious concomitant disorder; cerebral metastases requiring steroid treatment; a calculated creatinine clearance rate of <45 ml/min or presence of clinically detectable third space fluid collection. Patients were also ineligible if they had evidence of prior/concurrent malignancy other than in situ carcinoma of the cervix or adequately treated basal cell carcinoma of the skin or other malignancy treated ≥5 years previously without evidence of recurrence. All patients were required to provide written evidence of informed consent, and the protocol was approved by the ethics committee of each participating institution.

Pre-treatment investigations, performed within 3 weeks of commencing treatment, included full history and examination, assessment of weight and PS, and baseline radiology. In addition, the following evaluations were required no more than 2 weeks prior to treatment: laboratory tests including full blood count (FBC), coagulation profile, biochemistry (electrolytes, urea and creatinine, liver function tests, calcium, uric acid and phosphate); electrocardiograph; calculated creatinine clearance and measurement of vital signs. During treatment, FBC was taken once a week and biochemistry, urinalysis, vital signs and toxicity evaluation were taken once every 3 weeks.

**Treatment**

Pemetrexed was supplied as a lyophilised powder in 100 mg vials and reconstituted in 0.9% saline to form a clear solution containing 5–50 mg/ml. The drug was administered as a continuous infusion over 10 min at a dose of 600 mg/m² and courses were repeated every 3 weeks to a maximum of 12 cycles. Patients were retreated on schedule if the AGC was >1.5 × 10⁹/l and platelets >100 × 10⁹/l, and if the calculated creatinine clearance was >45 ml/min. Dose reduction of 25% occurred if the nadir granulocyte count was <0.5 × 10⁹/l and the nadir platelet count ≥50 × 10⁹/l, or if grade 2 mucositis occurred, after the previous course of pemetrexed. A 50% dose reduction occurred if the nadir granulocyte count was >0.5 × 10⁹/l, in association with a nadir platelet count of 25–49 × 10⁹/l, or if grade 3 or 4 mucositis occurred after the previous course of pemetrexed. A 75% dose reduction was undertaken if the granulocyte nadir was <0.5 × 10⁹/l and the nadir platelet count was 25–49 × 10⁹/l, or if the nadir platelet count was <25 × 10⁹/l, regardless of the nadir granulocyte count. Once a dose reduction had occurred, it was not permitted to re-escalate for subsequent courses. If a patient could not be retreated within 42 days from the last course of pemetrexed, they were excluded from further treatment. If Common Toxicity Criteria (CTC) grade 2 or greater cutaneous toxicity occurred, the patient was to receive prophylactic oral dexamethasone in subsequent cycles at a dose of 4 mg bd from the day prior to treatment for a total of 3 days. If a patient experienced protracted neutropenia (i.e. grade 4 for >7 days) it was planned that leucovorin rescue be administered. In addition, if short-acting non-steroidal anti-inflammatory drugs (NSAIDs) were being taken, it was required that these medications be stopped for 3 days, commencing the day before treatment. If long-acting NSAIDs were being taken, it was required that these be stopped for 7 days commencing 5 days before treatment with pemetrexed.
Assessment of study endpoints and statistical analysis
The initial study plan was to enrol up to 35 eligible patients from three Australian and two South African centres in a two-stage sequential fashion. Thirteen patients were to be enrolled in the first stage and if at least one patient responded to pemetrexed, another 22 patients were to be enrolled. If no patient of the first 13 responded the study was to be stopped. Subsequent to enrolment of the first 35 patients, an additional cohort of patients was included to more accurately define the confidence intervals of response. All patients were considered eligible for response if they fulfilled the eligibility criteria for study entry and received at least one cycle of pemetrexed. Response was assessed after every two cycles of treatment using standard South West Oncology Group criteria. Response duration was defined as the time from treatment initiation to the appearance of objective evidence of disease progression. Stable disease was measured from commencement of treatment until disease progression. Overall survival was measured from the date of initial treatment to the date of death and was estimated by the Kaplan–Meier method. All patients receiving at least one cycle of pemetrexed were assessable for toxicity and these were graded according to CTC.

Results
From April 1996 to July 1998, 59 patients received treatment with pemetrexed. The patient demographic data are summarised in Table 1.

Toxicity
The 59 patients received a median of four cycles of therapy (range 1–12 cycles). Six patients received a single cycle of pemetrexed before discontinuing treatment. In four of these, all with a pre-treatment PS of 2, treatment was stopped due to rapid disease progression. In the other two patients, treatment was discontinued on the basis of an adverse event. These consisted of a cerebrovascular accident and grade 4 diarrhoea, with the latter thought to be treatment related. Five other patients discontinued treatment following an adverse event after a range of 2–11 cycles of pemetrexed. In only one of these, a febrile episode, was the chemotherapy possibly implicated. The median dose of pemetrexed delivered was 600 mg/m². In 13 patients (22%) dose reduction was required due to toxicity (rash, one patient; stomatitis or mucous membrane disorder, six patients; haematological toxicity, four patients; diarrhoea, nausea, fever, asthenia, one patient each). Dose delay occurred in 19 patients, 11 for patients’ convenience and eight for toxicity (one patient each for decreased creatinine clearance, pharyngitis, severe constipation, pneumonia, vomiting, rash, stomatitis and infection). All patients were assessable for toxicity. The principal toxicities experienced by patients in this study are listed in Tables 2 and 3. Grade 3/4 neutropenia occurred in 25 patients (42%), but was not frequently complicated by febrile neutropenia, with grade 3 infection occurring in only two patients (3%) and grade 4 infection not seen. Only three patients (5%) experienced grade 3/4 thrombocytopenia, one of whom required platelet transfusion.

The liver function abnormalities observed were all clinically asymptomatic and principally manifest by elevations in serum ALT with parallel, but less significant, changes in AST. Eight (14%) and three patients (5%) had grade 3 elevations in ALT and AST, respectively. Abnormalities in serum alkaline phosphatase [two patients grade 3 (5%)] and γ-glutamyl transferase were less significant and only occasionally was the serum bilirubin elevated. The abnormalities in hepatic biochemistry were self-limited and settled both with continued treatment and on cessation of therapy, and did not necessitate dose reduction and/or delay.

Eighteen patients (31%) experienced grade 3/4 cutaneous toxicity. In two additional patients there was evidence of asymptomatic diffuse hyperpigmentation of the upper body that resolved on cessation of treatment. In only two cases did the skin toxicity affect ongoing patient treatment, with one delay for rash and one dose reduction by 50%; this toxicity improved with prophylactic treatment with dexamethasone. All skin changes completely resolved on cessation of therapy.

Grades 3/4 nausea and vomiting occurred in eight (14%) and five (9%) patients, respectively, and were easily managed.
with simple anti-emetics such as metoclopramide. In addition, grades 3/4 stomatitis and diarrhoea occurred in only three (5%) and two (3%) patients, respectively.

### Response

Of the 59 patients treated with pemetrexed, 57 were assessable for response. Two patients were subsequently deemed ineligible, one following the appearance of a colonic tumour of identical histology to a previously biopsied pulmonary lesion, and another who on review did not fulfil the entry criteria. Nine patients achieved a partial response [response rate (RR) of 15.8%; 95% confidence interval (CI) 7% to 28%], while in another 27 patients (47%) there was stable disease. One of 18 patients (5%) with a PS of 2 developed a response to pemetrexed compared, with eight of 40 with a PS of 0 or 1 (20%). Three of the patients achieving a response had stage III (one with stage IIIA, two with stage IIIB) disease while the other six had stage IV disease. The median duration of response was 4.9 months, the median time to disease progression 4.4 months and the median survival 7.2 months. The probability of surviving 12 months was 32%.

### Discussion

This study confirms the single-agent activity of pemetrexed in chemotherapy-naïve patients with advanced NSCLC. The RR of 16% (95% CI 7% to 28%) overlaps with that recently reported by Rusthoven et al. [10] (RR 23.3%; 95% CI 9.9% to 42.3%), from a Canadian trial of pemetrexed in chemotherapy-naïve patients with incurable NSCLC involving 33 patients. It was initially of identical design to the current study; however, the dose was reduced to 500 mg/m2 after the first three patients had been treated because of toxicity experienced in the lung study and in a colorectal trial of pemetrexed being performed in the same unit [10, 11]. The patient population was similar to the current study with a predominance of patients with adenocarcinoma (55%) and stage IV disease (76%), although only one patient (3%) in the Canadian trial had a PS of 2 compared with 19 patients (32%) in the current study, and this could explain the difference in RRs [10].

These results are also similar to the single-agent response rates reported for other new agents being used in NSCLC, including gemcitabine, vinorelbine, paclitaxel, docetaxel and irinotecan. The lack of response in the PS 2 patients is also consistent with data from studies of these other drugs which demonstrate that, apart from gemcitabine, RRs in PS 2 patients rarely exceed 10%. In fact, in many recent studies in NSCLC, including the latter stages of the ECOG trial, the eligibility criteria have been restricted to patients with a PS of 0 and 1 [4].

Unlike the Canadian study, the planned dose of pemetrexed 600 mg/m2 was able to be delivered in the current trial without unacceptable toxicity. The incidence of grades 3/4 neutropenia was 39% in the Canadian study compared with 41% in the current study, and infection was uncommon in both studies [10]. Cutaneous toxicity was less frequent in the current study, with 31% of patients experiencing grades 3/4 cutaneous toxicity compared with 39% in the Canadian study, although 10% of patients in the current study developed grade 4 cutaneous toxicity, which did not occur at the lower dose. However, the routine adoption of prophylactic oral dexamethasone given at a dose of 4 mg twice daily, the day before, day of and day after treatment, appeared to substantially improve patient tolerance of cutaneous toxicity. The incidence of nausea and vomiting were comparable in the two studies and were not a significant clinical problem. In addition, in neither study was there a significant incidence of stomatitis or diarrhoea, which are major clinical problems with other folate-based drugs such as methotrexate and raltitrexed, especially when combined with neutropenia.

Asymptomatic abnormalities of hepatic transaminases were seen in 80% of patients treated and in 14% there were eleva-
tions of to up to 20-fold of normal values. As has been reported with other folate-based drugs such as CB3717 and raltitrexed, it was possible to maintain dose intensity and schedule of pemetrexed without adversely affecting transaminase levels [12, 13]. On the contrary, there was a fall in transaminase levels despite continued treatment with pemetrexed. There was no evidence of progressive hepatic impairment and other indices of hepatic function, such as the prothrombin time and serum albumin level, remained normal. It is important to appreciate this clinical scenario as there is a risk of erroneously attributing the liver function abnormalities to progressive hepatic malignancy or inappropriately stopping or delaying treatment.

In more recent studies involving pemetrexed, routine administration of folic acid and vitamin B₁₂ supplements was received by all patients, commencing 1 week prior to chemotherapy. This treatment has been utilised to improve the ‘functional folate status’ of patients prior to receiving pemetrexed. Patients with a poor functional folate status, reflected by elevated baseline plasma homocysteine concentrations, have been shown to experience worse toxicity with pemetrexed, especially grades 3 and 4 myelosuppression, mucositis and diarrhoea [14]. The addition of vitamin supplementation has been demonstrated to significantly decrease the incidence of these toxicities and also drug-related deaths [15].

In summary, pemetrexed appears to have significant single-agent activity in patients with NSCLC. There is a potential for non-cross-resistance between this agent and many of the other commonly used anticancer drugs, and in particular, pemetrexed should not be subject to resistance from the various multidrug resistance mechanisms. Evidence for non-cross resistance of pemetrexed in NSCLC has been suggested by the encouraging preliminary results of a multi-centre study performed in patients who had received prior chemotherapy [16]. Combination studies with other active agents, such as paclitaxel, docetaxel, irinotecan, vinorelbine, cisplatin and gemcitabine, are being pursued as is the activity of pemetrexed when used as second-line therapy in patients with NSCLC. The final results of two trials combining cisplatin and pemetrexed have recently been published and reported response rates of 39–45% and median survivals of 8.9–10.8 months for patients with chemotherapy-naive stage IIIB or IV NSCLC [17, 18]. These data further confirm the promise of pemetrexed in the treatment of NSCLC.

References


