Gemcitabine/Alimta in Locally Advanced or Metastatic Non–Small-Cell Lung Cancer

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The search for new combination chemotherapeutic regimens for the treatment of non–small-cell lung cancer is motivated not only by the desire to increase the objective tumor response and survival rates, but also by the desire

Introduction

Gemcitabine (Gemzar) is a nucleoside antimetabolite analog of deoxycytidine that acts as a competitive substrate for incorporation into DNA. Clinical experience indicates that this compound has broad activity in a variety of solid tumors.[1] The phase II experience with gemcitabine in non–small-cell lung cancer (NSCLC) has shown that the overall objective response rate in six trials in the United States, Europe, and Japan with nearly 500 evaluable patients who received gemcitabine as first-line therapy is greater than 20% (mean = 20.6%; range 3%-26%).[2-8] These single-agent gemcitabine phase II trials are summarized in Table 1. The response rate was 19% in 83 patients with relapsing or refractory advanced NSCLC who received gemcitabine as second-line therapy.[9] However, most of these responses occurred in chemosensitive patients.

Alimta is a novel multitargeted antifolate that causes inhibition of at least three enzymes: thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycaminide ribonucleotide formyltransferase (GARFT).[10-12] Based on phase I trials, it was determined that the recommended phase II dosing regimen of Alimta was 600 mg/m² every 21 days.[13-15] However, this was reduced to 500 mg/m² early in phase II development due to unexpected toxicity. The early clinical experience with Alimta demonstrated its efficacy in breasts with NSCLC.[17,18] However, when Alimta was used as a second-line therapy, the response rate in patients previously treated with non–cisplatin (Platinol)-based regimens was 16%, compared with 9% in patients previously treated with cisplatin-based regimens.[19]

Phase I Study of Gemcitabine/Alimta in Solid Tumors

Clonogenic studies using HCT-8 colon carcinoma cell lines showed cytotoxic synergy when Alimta exposure was preceded by gemcitabine exposure.[20] As a result, a phase I study of the combination was conducted by Adjei and colleagues at the Mayo Clinic in patients with solid tumors.[16] The main objectives of the study were to determine: (1) the maximum-tolerated dose of each drug in combination; (2) the dose-limiting toxicity; (3) the recommended dose; (4) the presence of any antitumor activity; and (5) any pharmacokinetic interactions between the two drugs.

In the first cohort of 35 patients, gemcitabine was administered on days 1 and 8, and Alimta on day 1. These regimens were given every 21 days. There were 21 episodes of grade 4 neutropenia in the 35 patients in this cohort. Neutropenia led to a reduction in the day-8 gemcitabine dose in more than 50% of cycles. Other side effects included mild-to- moderate arthralgia, nausea, vomiting, fever, rash, and fatigue. Objective clinical responses were observed in seven (20%) patients: two with lung cancer, two with gallbladder disease, one with mesothelioma, one with ovarian cancer, and one with an unknown neoplasm.

In a second cohort of 21 patients, gemcitabine was administered on days 1 and 8, and Alimta on day 8 (instead of day 1) 90 minutes after the dose of gemcitabine. Once again, the regimens were given every 21 days. With this slightly modified regimen, there were only eight episodes of grade 4 neutropenia. Objective clinical responses were observed in six patients (28.6%): three with colorectal disease, one with lung cancer, one with ovarian cancer, and one with unconfirmed breast cancer.

Based on the above study, the recommended phase II dose was gemcitabine 1,250 mg/m² and
Phase II Trial of Gemcitabine/Alimta in Locally Advanced or Metastatic NSCLC

Because the phase I trials of gemcitabine/Alimta in patients with mixed solid tumors suggested that this combination may be useful in patients with NSCLC, a two-stage, phase II trial of gemcitabine/Alimta in locally advanced or metastatic NSCLC is currently being conducted at the Johns Hopkins Oncology Center, Baltimore, Maryland; University of Colorado Cancer Center, Denver, Colorado; and the Institut Gustave Roussy, Villejuif, France.

Study Objectives
The present ongoing trial is the first phase II study to evaluate the activity of gemcitabine in combination with Alimta in NSCLC. Secondary objectives are to assess: (1) qualitative and quantitative toxicity; (2) changes in the Lung Cancer Symptom Scale (LCSS) scores; and (3) the prognostic value of the vitamin metabolite status of the patients. The latter will be assessed by determination of homocysteine, cystathionine, methylmalonic acid, and methylcitrate levels within 7 days of study enrollment and following completion of the study. Since June 1999, 27 patients have been recruited into this two-stage study. It is expected that 60 patients will be enrolled. However, the study can be terminated early if, after 30 evaluable patients have been enrolled, treatment proves inefficacious or there is unacceptable toxicity. The study was designed to include ≥ 15 patients with stage IIIB NSCLC, and the remainder with stage IV disease.

Eligibility Criteria
To be eligible for study entry, patients are required to be at least 18 years of age and to have a histologic or cytologic diagnosis of bidimensionally measurable NSCLC. They must also have adequate bone marrow, hepatic and renal function, and a World Health Organization (WHO) performance status of either 0 or 1. Patients with documented brain metastases are not eligible for inclusion. Also excluded are patients who have (1) lost >10% of their body weight during the 6 weeks prior to study entry; (2) have received systemic chemotherapy or radiation therapy to lesion being measured to evaluate response unless clearly progressing; or (3) are taking salicylates or other nonsteroidal anti-inflammatory drugs (NSAIDs). Patients taking NSAIDs need to discontinue the drugs at least 2 days prior to Alimta dosing, or at least 5 days prior if the agent has a long half-life. This is because Alimta may compete with aspirin or other NSAIDs for renal tubular secretion, thereby decreasing Alimta clearance and predisposing patients to severe toxicity. Patients are also excluded if they have an active infection, second primary malignancy (except in situ carcinoma of the cervix, nonmelanomatous skin cancer, or other malignancy treated at least 5 years before entering the study with no evidence of recurrence), or cannot give informed consent.

Dosing Regimen
Given the results of the phase I trial previously described, the drug regimen being used in this phase II study is gemcitabine 1,250 mg/m² administered intravenously over 30 minutes on days 1 and 8 plus Alimta 500 mg/m² intravenously (IV) administered over 10 minutes on day 8 approximately 90 minutes after gemcitabine. This regimen is repeated every 21 days for six cycles, or for two cycles after the patient’s response is confirmed. Dexamethasone (Decadron) 4 mg (or an equivalent corticosteroid) is given orally twice-daily 1 day before, the day of, and 1 day after each dose of Alimta. Table 2 shows the dose modification schedule used in the study to prevent hematologic toxicity. In patients with grade 3 toxicity whose nadir absolute neutrophil count (ANC) is \(0.5 \times 10^9/L\) to \(9 \times 10^9/L\) and whose platelet counts are \(25.0 \times 10^9/L\) to \(49.9 \times 10^9/L\), it is recommended that the day-8 dose of gemcitabine/Alimta be withheld until the toxicity resolves. Treatment with the day-1 dose may then resume following resolution of toxicity. A similar approach is being used in patients with grade 4 toxicity whose nadir ANC is \(< 0.5 \times 10^9/L\) and whose platelet counts are \(< 25.0 \times 10^9/L\), with the exception that treatment for them should be resumed at 50% of the day-1 dose. Treatment may be delayed for up to 35 days in cases of hematologic toxicity. As shown in Table 3, day-1 dose modifications should be based on the ANC nadirs and the percent of platelets compared to the preceding cycle. Patients whose nadir ANC is \(\geq 0.5 \times 10^9/L\) and whose platelet counts are \(\geq 50% \times 10^9/L\) of the previous count may resume using the full day-1 dose of gemcitabine/Alimta once the hematologic toxicity resolves. Those whose nadir ANC is \(< 0.5 \times 10^9/L\) and whose platelet counts are \(\geq 50% \times 10^9/L\) of the previous count should receive 75% of the prior day-1 dose, as should those whose nadir ANC is \(> 0.5 \times 10^9/L\) and whose platelet counts are 25% to
49% \times 10^9/L of the previous cycle. Patients whose nadir ANC is < 0.5 \times 10^9/L and whose platelet counts are only 25% to 49% \times 10^9/L of the previous count should only receive 50% of the day-1 dose when therapy is resumed. This same guideline pertains to patients with variable nadir ANCs whose platelet counts are < 25% \times 10^9/L of the previous count.

The dose modification recommendations for Alimta in patients with mucositis are based on standard criteria (Table 4). The full dose of Alimta may be used in patients with grade 0 to 2 mucositis in a previous cycle, but should be decreased by 50% in patients who experienced grade 3 or 4 mucositis. Use of Alimta should be discontinued after two dose reductions in patients with recurrent grade 3 or 4 mucositis.

**Concomitant Therapy**

Patients with grade 4 neutropenia or thrombocytopenia, or grade 3-4 mucositis, are permitted to use leucovorin during the course of the study. The recommended dosing regimen is 100 mg/m² IV q6h on day 1, followed by 50 mg/m² q6h for a total of 8 days. Granulocyte colony-stimulating factor (G-CSF) may be used if the ANC < 0.5 \times 10^9 L for \geq 3 days, or if there is neutropenic fever or documented infection while neutropenic, but may not be used for prophylaxis. No salicylates or NSAIDs are permitted 2 days before, during, and 2 days after treatment with Alimta.

**Conclusions**

Given the toxicity associated with cisplatin-containing regimens, non–cisplatin-containing regimens warrant study. Such regimens currently being assessed include gemcitabine-containing combinations. Since both gemcitabine and Alimta are effective as single-agents in the treatment of NSCLC as demonstrated in phase II studies, the combination of Alimta/gemcitabine should be studied for its efficacy and possibly reduced toxicity in patients with NSCLC. An ongoing phase II study of Alimta/gemcitabine is currently being conducted. If effective, a phase III trial should be performed to compare this regimen with one of several [standard] therapies used to treat stage IIIB and metastatic NSCLC.

**References:**


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