Incorporation of Pemetrexed (Alimta) Into the Treatment of Non–Small Cell Lung Cancer (Thoracic Tumors)

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Lung cancer is the leading cause of cancer death in the United States and throughout the world. The overall 5-year survival rate for lung cancer is dismal: 14% in the United States and even lower in other parts of the world. Recent developments in the armamentarium of chemotherapeutic agents for lung cancer have shown that two-drug combinations improve survival, relieve symptoms, and improve quality of life; however, complete response rates are still approximately 1% in stage IV disease and less than 20% of advanced stage patients survive 2 years. Therefore, improved therapeutic agents that increase efficacy are sorely needed. Most lung cancers overexpress thymidylate synthase and a variety of genes involved in cell cycle regulation. Previous studies have shown that some inhibitors of DNA synthesis (eg, gemcitabine) can improve the survival of advanced lung cancer patients, especially when combined with other agents such as cisplatin. The multitargeted antifolate, pemetrexed (Alimta; Eli Lilly and Co, Indianapolis, IN) was developed because it inhibits multiple enzymes involved in DNA synthesis including thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyl transferase. The early studies of pemetrexed showed that the important dose-limiting toxicities were myelosuppression, mucositis, and diarrhea, all of which are common with any antimetabolite. Subsequent studies described in this article will show that these toxicities can be significantly reduced by the use of vitamin supplementation with folate and B_{12}, and that pemetrexed has considerable activity in non–small cell lung cancer and mesothelioma.

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LUNG CANCER is the leading cause of cancer death in both men and women in the United States and many developed countries. Lung cancer accounts for 28% of all cancer deaths in the United States.[1] The non–small cell lung cancers (NSCLCs) (adenocarcinoma, squamous cell carcinoma, and large-cell undifferentiated carcinoma) account for 75% to 80% of all lung cancers.[2] About one third of NSCLC patients present with metastatic disease (stage IV) at the time of diagnosis, and more than half present with stage IIIB or IV.[2]

Before 1990, no systemic therapy had been proven to increase the survival of these patients. Subsequently, cisplatin-based chemotherapy was shown to improve survival, increasing median survival by around 2 months and improving the 1-year survival rate from 15% to 25%.[2,3] More recently, several new agents including gemcitabine (Gemzar; Eli Lilly and Co, Indianapolis, IN), vinorelbine, paclitaxel, and docetaxel, were shown to be active and some have improved the survival of advanced-stage NSCLC patients.[2] Two-drug combinations combining these agents with one another or with cisplatin or carboplatin improved survival compared with single-agent cisplatin.[4,5] Randomized trials have shown that several of these two-drug combinations have comparable efficacy.[6,7] Nonetheless, even the best of these two-drug combinations produces responses in fewer than half of the patients, with complete responses in only 1%, and more than 80% of patients die within 2 years of diagnosis.[2,7] New agents, especially those with minimal or little myelosuppression, are sorely needed.

PRECLINICAL TRIALS OF PEMETREXED

The multitargeted antifolate pemetrexed (Alimta; Eli Lilly and Co) possesses mechanisms of action that inhibit multiple enzymes involved in DNA synthesis, including thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyl transferase. Pemetrexed inhibited the growth of a large panel of human cancer cells lines, including lung cancer cells in vitro[8] and in vivo in athymic nude mice.[9] Combination studies showed additive or synergistic growth inhibition when pemetrexed was combined with several established chemotherapeutic agents such as gemcit-

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Table 1. Tumor Growth Delay by Alimta, Cisplatin, Gemcitabine, Paclitaxel, and the Combinations in Human A549 Adenocarcinoma Cells in Athymic Mice[9]

Therapy	Average Growth Delay (days)
Pemetrexed	8
Gemcitabine	7
Cisplatin	6
Paclitaxel	7
Alimta and Cisplatin	18
Alimta and Gemcitabine	17
Alimta and Paclitaxel	15

abine, cisplatin, and paclitaxel (Table 1).[9] For example, when compared with the control growth of A549 tumors, pemetrexed produced an average growth delay of 8 days. The combination of pemetrexed with cisplatin, gemcitabine, or paclitaxel increased the average growth delay to 15 to 18 days (see Table 1).

PHASE I TRIALS OF PEMETREXED

Phase I trials of pemetrexed explored several schedules including an every 3-week schedule,[10] a weekly schedule,[11] and a daily for 5 consecutive days every-3-week schedule.[12] Objective responses were seen with several schedules, including four partial responses (two each in advanced pancreatic and colorectal cancers) and six minor responses (colorectal cancer) on the every-3-week schedule.[10] This schedule was also the most convenient and produced consistent toxicity. The dose-limiting toxicity (DLT) on this schedule developed at a dose of 700 mg/m^2, and the recommended phase II dose was 600 mg/m^2.[10] Dose-limiting toxicities consisted of myelosuppression, mucositis, and diarrhea. Skin toxicity developed in a minority of patients. The pre- and postadministration of decadron daily for 3 days around the pemetrexed dose seemed to reduce the frequency of skin toxicity. The severity of nausea and vomiting were mild, even without steroids. Toxicities encountered during early phase II trials with the dose of 600 mg/m^2 every 3 weeks led to a subsequent decrease in the recommended phase II dose to 500 mg/m^2.

PHASE II TRIALS OF PEMETREXED IN ADVANCED NON–SMALL CELL LUNG CANCER

Two studies evaluated the role of pemetrexed in patients with advanced NSCLC who had not received prior chemotherapy. The results are summarized in Table 2. In these respective trials that were conducted in Canada[13] and South Africa/Australia,[14] similar results were produced. In the Canadian trial, Rusthoven et al[13] used the initial dose of 600 mg/m^2. After the first three patients had been enrolled, the dose was reduced to 500 mg/m^2 in the remaining 30 patients. This was based on the combined toxicity of 12 patients enrolled onto this study and a Canadian phase II study of pemetrexed in advanced colorectal cancer.[15] The objective response rate was 23% among 30 patients evaluable for response (all 33 assessable for toxicity), and the median survival was 9.2 months. The most frequent severe toxicity was grade 3/4 neutropenia, which developed in 39% of the patients. In the South African/Australian trial, Clarke et al[14] used a dose of 600 mg/m^2 in all 59 patients. The objective response rate was 16% among 57 evaluable patients. Median survival was 7.2 months, and 32% of the patients were alive at 1 year. The toxicity rates were similar to the Canadian trial despite the slightly higher dose of pemetrexed. Overall, the response rate was 19.5%

Table 2. Summary of Phase II Studies of Single-Agent Pemetrexed in Advanced Non–Small Cell Lung Cancer

Study	Dose	No. of Patients (Evaluable)	Objective Response, n (%)	Median Survival (mos)	1-Year Survival (%)*	Grade 3/4 Neutropenia (%)†
Rustoven et al[13] (Canada)	600/500	33 (30)	7 (23)	9.2	25	39
Clarke et al[14] (Australia/South Africa)	600	59 (57)	9 (16)	7.2	32	42

*Percentage of patients alive at 1 year.
†Percentage of patients.

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Table 3. Phase II Trial of Pemetrexed in Second-Line Therapy of Advanced Non–Small Cell Lung Cancer[16]

Group	No. of Patients	Objective Response, n (%)	Median Survival (mos)	1-Year Survival (%)*	Grade 3/4 Neutropenia (%)†
Prior cisplatin	45	4 (9)	6.1	19	35
No cisplatin	33	5 (15)	4.1	24	

* Percentage of patients alive at 1 year.
† Percentage of patients.

in these two trials and the median survival was between 7.2 and 9.2 months. The results are similar to the most active agents, including gemcitabine, paclitaxel, and docetaxel.

An additional trial evaluated the role of pemetrexed in patients with advanced NSCLC who had progressed during or within 3 months of completing prior chemotherapy.[16] The results of this trial are summarized in Table 3. Among the 78 evaluable patients in this trial, 44 had received therapy that included a platinum agent, and 33 had not. The objective response rate was higher in the platinum-naive patients (15% *v* 9%). Overall, the objective response rate was 9% (compared with a 19% response rate observed in previously untreated patients). Survival results were also excellent, with median survivals of 6.1 and 4.1 months in the respective platinum-pretreated and platinum-naive groups. Results are similar to the phase II results reported with docetaxel in the second-line setting. Pemetrexed was well tolerated in this group, with 35% of patients experiencing grade 3/4 neutropenia. The excellent results noted in this trial led to the institution of an ongoing phase III randomized trial comparing pemetrexed to docetaxel in NSCLC patients who had previously received chemotherapy.

PHASE I TRIALS OF CISPLATIN PLUS PEMETREXED

The preclinical synergy between pemetrexed and cisplatin combined with the activity of each agent in NSCLC made it logical to test the combination. A phase I trial evaluated the schedule of pemetrexed and cisplatin given every 3 weeks.[17] When both drugs were administered on day 1, the dose-limiting toxicity was neutropenia. Mucositis, nausea/vomiting, and diarrhea were also observed, but were well controlled with supportive measures. The maximum tolerated dose was pemetrexed 600 mg/m^2 with cisplatin 100 mg/m^2. Objective responses were noted in this phase I trial, including one patient with NSCLC and five patients with mesothelioma. The recommended doses for phase II trials were pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2, both given on day 1 every 3 weeks.

PHASE II TRIALS OF PEMETREXED PLUS CISPLATIN

Two phase II trials[18,19] evaluating the combination of pemetrexed plus cisplatin in previously untreated patients with advanced NSCLC were conducted using pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 given every 3 weeks. The results are summarized in Table 4. In the study from Canada, Shepherd et al[18] reported an objective response rate of 45% among 29 evaluable patients. A similar response rate (39%) was noted among 36 patients in a European trial by Manegold et al:[19] Median survival in the two studies was 8.9 and 10.9 months, and approximately 50% of patients were alive at 1 year in both trials. The 33% and 59% rates of grade 3/4 neutropenia were higher than with either single agent, but were of shorter duration and were relatively well tolerated. There were no septic deaths. These response and survival rates are as good as those reported in phase II trials by any "standard" two-drug combination.[2]

PHASE III TRIAL OF PEMETREXED PLUS CISPLATIN VERSUS CISPLATIN IN MESOTHELIOMA

Based on the finding of responses to pemetrexed plus cisplatin in mesothelioma patients in the phase I setting, a randomized phase III trial comparing cisplatin with pemetrexed plus cisplatin has been completed. The results, which should be available in 2002, are eagerly awaited.

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Table 4. Phase II Trials of Cisplatin Plus Pemetrexed in Previously Untreated Advanced Non-Small Cell Lung Cancer

Study	No. of Patients (Evaluable)	Objective Response, n (%)	Median Survival (mos)	1-Year Survival (%)*	Grade 3/4 Neutropenia (%)†
Shepherd et al[18] (Canada)	31 (29)	13 (45)	8.9	49	33
Manegold et al[19] (Europe)	36 (36)	14 (39)	10.9	50	59

* Percentage of patients alive at 1 year.
† Percentage of patients.

PHASE I TRIALS OF PEMETREXED PLUS GEMCITABINE

The preclinical synergy noted between pemetrexed and gemcitabine combined with the known clinical activity of each agent in advanced NSCLC provided a rationale to test these two drugs in combination. Adjei et al[20] at the Mayo Clinic used two different schedules in a phase I trial. In the first cohort (n = 35), gemcitabine 1,000 and 1,250 mg/m^2 was given on days 1 and 8, with pemetrexed 200 to 600 mg/m^2 given 90 minutes after gemcitabine on day 1. Cycles were repeated every 3 weeks. In the second cohort (n = 21), gemcitabine was also given on days 1 and 8, but pemetrexed was administered on day 8; cycles were also given every 3 weeks. The schedule on which pemetrexed was delivered on day 8 produced less hematologic toxicity than the schedule with day 1 pemetrexed administration, permitting a higher gemcitabine dosage in this schedule. The days 1 and 8 gemcitabine maximum tolerated dose was 1,250 mg/m^2 combined with pemetrexed 500 mg/m^2 on day 8, every 3 weeks. Overall, there were 13 objective responses: NSCLC (3), colorectal cancer (3), cholangiocarcinoma (2), ovarian carcinoma (2), mesothelioma (1), breast cancer (1), and adenocarcinoma of unknown primary site (1). The recommended dose for the phase II study was gemcitabine 1,250 mg/m^2 days 1 and 8 and pemetrexed 500 mg/m^2 (90 minutes after gemcitabine) on day 8, every 3 weeks.

PHASE II TRIAL OF PEMETREXED PLUS GEMCITABINE

Based on the results of the phase I combination trial described previously, an international phase II trial of pemetrexed plus gemcitabine was conducted in North America (John Hopkins University, University of Colorado, Denver) and Europe (Institut Gustave-Roussy, Villejuif, France).[21] In the initial phase of this study, the pemetrexed dose was 500 mg/m^2 given on day 8, the gemcitabine dose was 1,250 mg/m^2 administered on days 1 and 8, and there was no vitamin supplementation. When data from other clinical studies indicated that daily administration of 350 to 600 μg of folic acid and vitamin B_{12} every 9 weeks could reduce the toxicity of pemetrexed, and data from a preclinical study suggested that this could potentially be achieved without reducing effectiveness (see below), the study was modified to provide folic acid and vitamin B_{12}. The final study results are not yet available. However, the study had a two-stage design with an early stopping rule if the response rate was less than 20%, and the study completed the planned accrual.

EFFECTS OF FOLATE AND B_{12} STATUS ON PEMETREXED TOXICITY

Analysis of many earlier pemetrexed studies showed that pretreatment folate and B_{12} status of patients were highly correlated with toxicity.[22] In these studies, folate status was assessed by serum homocysteine levels, and B_{12} status by serum methylmalonic acid levels. Patients with high homocysteine levels (associated with folate deficiency) had significantly higher rates of severe myelosuppression, mucositis, and febrile neutropenia compared with patients with lower homocysteine levels. There was also a correlation between low methylmalonic acid levels and increased toxicity. Subsequently, data from a randomized trial comparing pemetrexed plus cisplatin with cisplatin alone in mesothelioma patients showed an excess of toxic deaths and severe toxicity on the pemetrexed plus cisplatin arm. Preclinical data

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Table 5. Toxicities in Trials of Pemetrexed With and Without Vitamin Supplementation[24,25]

Toxicity	No Folic Acid/B_{12} (n = 394), %	+ Folic Acid/B_{12} (n = 196), %	*P* Value
Drug-related death	4.2	1.4	.006
Grade 4 neutropenia	28	9.0	
Grade 4 thrombocytopenia	6	1.0	
Grade 3/4 diarrhea	5	4	
Grade 3/4 mucositis	5	0.5	.0017
Any grade 4 hematologic or grade 3/4 nonhematologic*	33	12	

*Toxicities include grade 4 neutropenia, grade 4 thrombocytopenia, grade 3/4 mucositis, grade 3/4 diarrhea, and grade 3/4 infection.

also became available that suggested that folate supplementation might reduce toxicity without reducing efficacy.[23] These data led to the institution of folic acid and B_{12} supplementation in all ongoing trials, including the mesothelioma trial. As shown in Table 5, folic acid and B_{12} supplementation has produced a highly significant reduction in the rate of severe toxicity (C. Niyikiza, personal communication, January 2002).[24] Vitamin supplementation is now standard in all pemetrexed trials. This supplementation is especially important in countries that do not require dietary supplementation, as required in the United States.

PHASE I TRIAL OF CARBOPLATIN PLUS PEMETREXED

The excellent results obtained with pemetrexed plus cisplatin, coupled with the greater convenience and reduced toxicity profile of carboplatin, led Calvert et al[25] to conduct a phase I trial of pemetrexed plus carboplatin. All patients accrued to this trial had mesothelioma and were chemotherapy-naive. The maximum tolerated dose was reported to be pemetrexed at 500 mg/m^2 and carboplatin dosed to an area under the concentration-time curve (AUC) of 6 (based on the Calvert Formula with ^{51}Cr-EDTA estimation of glycinamide ribonucleotide formyl transferase), each administered on day 1 of a 3-week cycle; the dose-limiting toxicity was reversible myelosuppression. The recommended dose for phase II trials was pemetrexed 500 mg/m^2 and carboplatin at an AUC of 5. These were given on a 3-week schedule with both drugs administered on day 1. No vitamin supplementation was used in this trial. Interestingly, the results in the mesothelioma patients were superior to the best reported in any historical series from this patient group. The overall response rate was 40% among 25 evaluable patients. No patients progressed during the first three cycles of therapy, and the median survival rate was 13 months.

SINGLE-AGENT PEMETREXED IN MESOTHELIOMA

Scagliotti et al[26] evaluated single-agent pemetrexed in 62 chemotherapy-naive patients with malignant pleural mesothelioma. Pemetrexed 500 mg/m^2 was administered by 10-minute intravenous infusion on day 1, every 3 weeks. After 21 patients had enrolled, vitamin supplementation (low-dose folic acid/vitamin B_{12}) was added to therapy to reduce the toxicity of pemetrexed. Nine patients achieved a partial response, for an overall response rate of 14.5%. To date, median duration of response is 10.8+ months, median time-to-progressive disease is 5.4 months, median survival time is 10.7 months, and the 1-year survival rate is 25%.

CONCLUSIONS

Pemetrexed is an active agent for NSCLC and mesothelioma. Single-agent responses occur in approximately 20% of chemotherapy-naive NSCLC[13,14] and 14.5% of chemotherapy-naive mesothelioma patients.[26] The survival results in the phase II single-agent pemetrexed studies in these diseases are as high as those produced by other known agents. The combination of pemetrexed plus cisplatin produces higher response rates in both NSCLC than is observed for either single agent, and the survival rates are superior to those reported in historic series with other doublet therapies. The rates of toxicity from pemetrexed are related to the dose and folate and B_{12} status of

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