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REVIEW

Pemetrexed as first-line therapy for non-squamous non-small cell lung cancer

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Abstract: Pemetrexed is a new cytotoxic agent that is a standard of care for the second-line treatment of non-small cell lung cancer (NSCLC) and in combination with cisplatin in treatment of malignat pleural mesothelioma. It has been studied in numerous phase II and III trials in combination with different drugs or as single agent. Recently, pemetrexed has been approved in combination with cisplatin for the first-line treatment of patients with locally advanced or metastatic NSCLC other than squamous cell histology. The toxicity is acceptable and similar to that of other NSCLC regimens. The postinduction maintenance therapy with pemetrexed is being evaluated in a phase III, double-blind, placebo-controlled study.

Keywords: pemetrexed, non-small cell lung cancer, non-squamous carcinoma, first-line setting

Introduction

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related death in both men and women in most of the Western world, with an estimated 900,000 deaths per year worldwide.[1] Occupational and environmental exposure to carcinogenic substances (eg, radon, asbestos, diesel exhaust fumes and metals) may increase the risk of developing lung cancer, but the risk is small compared with that associated with tobacco use.[2] Most patients (approximately 80%) present with locally advanced stage III or metastatic stage IV NSCLC and are ineligible for curative surgery.[3,4] The long-term prognosis for patients with NSCLC remains poor, the 5-year survival rate ranging from 8% to 15%.[5]

Some progress has been made in the treatment of advanced NSCLC during the past decade.[6] Chemotherapy with cisplatin-based regimens was shown to prolong survival, relieve symptoms in most cases, and improve quality of life. The introduction of several new agents, including paclitaxel, gemcitabine, and vinorelbine, offered hope for a better outcome because overall survival improved with combination regimens that included these new agents compared with cisplatin alone.[6] Phase III trials in NSCLC suggested that a plateau in clinical benefit has been reached with a median survival of 8 months. No specific regimen had superior therapeutic efficacy, as measured by overall survival.[7] The addition of bevacizumab to platinum doublets has added 2 months of survival time compared with chemotherapy alone.[8] Specifically an Italian phase III randomized trial comparing 3 platinum doublets also showed no difference in efficacy endpoints between the different treatment arms, leading to the conclusion that chemotherapy in NSCLC had reached a therapeutic plateau.[9]

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Clearly additional new therapies with an innovative mode of action, improved efficacy and reduced toxicity are warranted.

Pemetrexed: a novel multitargeted antifolate

Pemetrexed (Alimta®; Eli Lilly and Company) is a novel multitargeted antifolate that inhibits 3 enzymes: thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyl transferase.[10] These enzymes are involved in the synthesis of nucleotides, ultimately hindering RNA and DNA synthesis. Investigational studies have demonstrated the cytotoxic activity of this agent in a broad range of tumor types including NSCLC. These studies also showed that combinations of pemetrexed with cisplatin, gemcitabine and taxanes produced additive or synergistic cytotoxicity.[11] Recent studies in humans also showed that vitamin supplementation with B12 and folate reduced toxicity without nullifying the cytotoxic effects.[12] Nowadays the standard vitamin supplementation consists of oral folic acid at 350 to 1000 μg administered at least 5 continuous days prior to pemetrexed and continuing daily throughout therapy and vitamin B12 at 1000 μg administered intramuscularly prior to first dose of pemetrexed.[13]

Pemetrexed as first-line NSCLC treatment

Phase II clinical trials

Pemetrexed as single agent

Multiple phase II trials involving pemetrexed have been completed in patients with NSCLC.

The single-agent activity of pemetrexed in the first-line treatment of advanced NSCLC has been analyzed in 2 open-label, phase II trials.

In 1999 Rusthoven[14] enrolled 33 previously untreated patients with NSCLC to determine the response rate to single-agent pemetrexed 500 mg/m^2 every 21 days. The median patient age was 63 years. Among 30 patients evaluable for response, 7 had partial responses for response rate of 23%. Median survival was 9.2 months and 1-year survival rate was 25%. Grade 3–4 neutropenia was observed in 27% of patients, and 39% had grade 3–4 skin rash.

The other study was conducted in Australia and South Africa.[15] Fifty-nine chemotherapy-naive patients with advanced NSCLC received 600 mg/m^2 of pemetrexed. The response rate was 16%; median survival time was 7.2 months and 1-year survival rate was 32%. Grade 3–4 neutropenia was observed in 42% of patients and 31% had grade 3–4 skin rash. The study also revealed that 47 patients (80%) developed asymtomatic elevations in transaminase levels that returned to normal throughout the study.

More recently, another randomized phase II trial[16] evaluated single-agent pemetrexed 500 mg/m^2 or sequential pemetrexed 500 mg/m^2 and gemcitabine 1200 mg/m^2 in patients with NSCLC who were elderly (>70 years) or younger than 70 years and ineligible for platinum-based chemotherapy. Eighty-seven patients received treatment. Tumor response rates were 4.5% and 11.6% respectively for the pemetrexed and pemetrexed/gemcitabine arms. Median overall survival time was 4.7 months for the pemetrexed arm and 5.4 months for the pemetrexed/gemcitabine arms. Both hematological and non-hematological toxicities were mild. The study showed that single-agent pemetrexed and sequential pemetrexed/gemcitabine have moderate activity and are well tolerated as first-line treatment for advanced NSCLC in elderly patients or in patients unsuitable for platinum-based combination chemotherapy.

Pemetrexed platinum-based regimens

Clinical trials have also been conducted to evaluate front-line treatment with pemetrexed combined with a platinum agent.

Two phase II trials were conducted to evaluate the efficacy and safety of pemetrexed combined with cisplatin for advanced NSCLC.[17,18] The designs of these two trials were similar: pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2 on the first day of a 21-day cycle, without vitamin supplementation, but with dexamethasone prophylaxis. The first study was conducted in Germany and included 36 chemotherapy-naive NSCLC patients. Median patient age was 58 years. The overall response rate was 39%, with a median survival rate of 10.9 months. Fifty-nine percent of patients had grade 3–4 granulocytopenia while 17% had grade 3–4 thrombocytopenia.

The National Cancer Institute of Canada study enrolled 31 patients. Overall response rate was 45%, median overall survival was 8.9 months and 1-year survival rate was 49%. The regimen was well tolerated. Grade 3 or 4 granulocytopenia was seen in 7 and 4 patients, respectively; grade 3 or 4 anemia was seen in 5 and 1 patients, reaspectively.

These results demonstrate the clinical activity of the cisplatin/pemetrexed combination for patients with advanced NSCLC and did not demonstrate significant increases in toxicity.

Pemetrexed has also been investigated in combination with either carboplatin or oxaliplatin. In a phase II trial

80 patients were randomized to pemetrexed 500 mg/m^2 plus either carboplatin (area under the curve [AUC] 6) or oxaliplatin 120 mg/m^2 on day 1 of a 3-week cycle, for up to 6 cycles.[18] Low dose folic acid and vitamin B12 were provided. All efficacy outcomes measured were similar between the two combination doublets, and comparable to other combinations regimens, including cisplatin. However, the pemetrexed combination had a superior toxicity profile to the other platinum doublets.

In 2004 a single-institution, single-arm, phase II study demonstrated favorable activity with pemetrexed/carboplatin combination.[19] The trial was conducted in 50 patients with adavanced NSCLC. Patients were administered carboplatin AUC 6 and pemetrexed 500 mg/m^2 on day 1 every 21 days for a median of 6 cycles. The objective response rate was 29%, median time to tumor progression 4.6 months, median overall survival 13.4 months and 1-year survival 52%.

In 2005 Zinner[20] published an open study in which patients were treated with pemetrexed 500 mg/m^2 and carboplatin (AUC 6) on day 1 every 3 weeks. Main grade 3–4 toxicity was neutropenia (26%). Median time to progression was 5.4 months and overall survival 13.5 months, with a 1-year survival of 56% (Table 1).

Pemetrexed platinum-free regimens

Monnerat[21] reported results from a phase II trial of gemcitabine 1250 mg/m^2 on days 1 and 8, and pemetrexed 500 mg/m^2 on day 8 every 21 days.The investigators administered routine vitamin supplementation. Overall response rate was 15.5%, and median overall survival was 10.1 months. The 1-year survival rate was 42.6%. Grade 3–4 neutropenia occurred in 61.7% of patients.

Another phase II clinical trial was conducted to evaluate various dosing regimens for a combination of pemetrexed and gemcitabine.[22] Patients received pemetrexed followed by gemcitabine on day 1 and gemcitabine on day 8; or gemcitabine followed by pemetrexed on day 1 and gemcitabine on day 8; or gemcitabine on day 1 and pemetrexed followed by gemcitabine on day 8. The results demonstrated that the administration of pemetrexed on day 1 before gemcitabine on day 1 and 8 had the least toxicity, with efficacy similar to that of other administration schedules.

In 2006 Treat[23] evaluated the combination of pemetrexed 500 mg/m^2 on day 1 and gemcitabine 1250 mg/m^2 on day 1 and 8 every 21 days. All patients received folic acid, vitamin B12 and steroid prophylaxis. A total of 53 patients were enrolled. Median time to disease progression was 3.3 months and median survival was 10.3 months. The toxicity was acceptable and similar to that of other NSCLC regimens.

In a recent meta-analysis[24] of pemetrexed plus gemcitabine in first-line treatment of patients with advanced NSCLC, based on 4 trials, it was observed that the combination was efficacious and well tolerated. A phase I trial by Adjei[25] established the preferred sequence as 21-day cycles of gemcitabine 1250 mg/m^2 on days 1 and 8, and pemetrexed 500 mg/m^2 given 90 minutes after day 8 gemcitabine. Subsequent phase II studies in advanced NSCLC employed a 90-minute delay between gemcitabine and pemetrexed administration and demonstrated efficacy worthy of further study.[26,27]

Recently, a pharmacokinetic study conducted by Dy[28] found that the delay between gemcitabine and pemetrexed administration may be unnecessary.

West[29] conducted a phase II clinical trial in which chemotherapy-naive patients with late-stage NSCLC received gemcitabine 1250 mg/m^2 on days 1 and 8, with pemetrexed 500 mg/m^2 immediately after day 8 gemcitabine every 21 days for 6 cycles, and folic acid, B12, and steroid prophylaxis.

The trial demonstrated that administering day 8 pemetrexed immediately after gemcitabine does not appear to reduce therapeutic index.

In 2008 Dudek[30] conducted a phase I/II trial: the phase I study included patients with advanced tumors, whereas the phase II study included patients with locally advanced or metastatic NSCLC. Gemcitabine was infused over 30 minutes, followed by pemetrexed administered over 10

Table 1 Pemetrexed in combination with platinum in the first-line setting for NSCLC (phase II)

	MD Anderson trial[20]	European trial[18]	
Concomitant drugs	**Pemetrexed + Carboplatin**	**Pemetrexed + Carboplatin**	**Pemetrexed + Oxaliplatin**
No patients	50	39	41
ORR %	24.0	31.6	26.8
Survival (months)	13.5	10.5	10.5
PFS (months)	5.4	5.5	5.7

Abbreviations: ORR, overall response rate; PFS, progression free survival.

minutes on day 1 of a 14-day cycle. Treatment continued for 12 cycles or until disease progression. All patients received folic acid, vitamin B12, and steroid prophylaxis. Dudek demonstrated that twice-monthly gemcitabine and pemetrexed was well tolerated, with overall survival and clinical benefit indicating disease activity in NSCLC patients.

Pemetrexed has also been evaluated in combination with vinorelbine. In 2005 Clarke[31] conducted a phase I/II study which enrolled 37 patients who received pemetrexed 500 mg/m^2 and vinorelbina 30 mg/m^2. Median overall survival was 7.9 months, time to progression 4.4 months and median progression free survival 4.2 months. Main grade 3–4 toxicities reported were neutropenia (65%) and fatigue (8%).

Approved indications

Pemetrexed received in 2003 FDA approval for malignant pleural mesothelioma, based on a randomized, phase III, single-blind, multicenter trial that compared cisplatin alone versus cisplatin plus pemetrexed.[32] The patients (n = 448) were randomized to receive pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 or cisplatin alone at the same dose. The study demonstrated that pemetrexed significantly improves survival by 3 months when administered with cisplatin, with significant differences in overall response rate (41.3% vs 16.7% in the pemetrexed/cisplatin arm and cisplatin alone arm, $p < 0.0001$).

Pemetrexed was approved in 2004 as second-line therapy in patients with previously chemotherapy-treated advanced NSCLC based on a randomized, open-label, phase III trial.[33]

In this study 571 patients were randomly assigned to receive pemetrexed monotherapy (283 patients) or docetaxel monotherapy (288 patients). The trial showed that pemetrexed and docetaxel had comparable activity and efficacy, with median survival times of approximately 8 months in both arms, but pemetrexed was associated with significantly less hematological toxicity and alopecia.

Based on this study, pemetrexed should be preferred over docetaxel as standard second-line NSCLC treatment.

Phase III clinical trials combined with platinum

At the XX ASCO meeting, Gronberg[34] presented the data of a randomized study evaluating pemetrexed 500 mg/m^2 plus carboplatin AUC 5 day 1 or gemcitabine 1000 mg/m^2 day 1 and 8 plus carboplatin AUC 5 day 1. The investigators enrolled 437 patients. Of patients enrolled, 22% had poor performance status (PS = 2), and 18% were >75 years old, so the starting dose administered to elderly patients was reduced to 75% and the number of cycle permitted was 4. Median overall survival was 7.3 months and 7 months respectively in the pemetrexed/carboplatin arm and gemcitabine/carboplatin arms.

In 2008 Scagliotti[35] reported results from a randomized, non-inferiority, phase III study. From July 2004 to December 2005, 1725 chemotherapy-naive patients with advanced NSCLC were assigned to receive either cisplatin 75 mg/m^2 on day 1 plus gemcitabine 1250 mg/m^2 on days 1 and 8 (cisplatin/gemicitabine arm) or cisplatin 75 mg/m^2 plus pemetrexed 500 mg/m^2 on day 1 (ciplatin/pemetrexed arm), every 3 weeks for a maximum of 6 cycles. All patients received oral folic acid, vitamin B12 and dexamethasone prophylaxis. The primary objective was to compare the overall survival between 2 regimens (Table 2).

Overall survival for patients in the cisplatin/pemetrexed group was non-inferior to the overall survival of patients in the cisplatin/gemcitabine group. Survival rates at 12 months were 43.5% and 41.9% for cisplatin/pemetrexed and cisplatin/gemcitabine respectively. Progression free survival and time to progressive disease were also non-inferior. For the cisplatin/pemetrexed doublet both hematologic and non-hematologic toxicities were significantly favorable.

Grade 3–4 neutropenia occurred in 15% of patients with pemetrexed and in 27% of patients with cisplatin/gemcitabine. Anemia was observed in the 6% of patients in the cisplatin/pemetrexed arm and in the 10% of patients in the cisplatin/gemcitabine arm. Patients in the cisplatin/gemcitabine arm required significantly more transfusions and supportive care interventions than did patients in the cisplatin/pemetrexed arm.

Deaths attributed to study drug toxicity were low and were similar between arms (9 patients, 1%, for the cisplatin/pemetrexed arm, and 6 patients, 0.7%, for the cisplatin/gemcitabine arm).

Table 2 Histologic type of patients included in phase III CP vs CG in the first-line setting for NSCLC[27]

	CP N = 862	CG N = 863
Adenocarcinoma	436 (50.6%)	411 (47.6%)
Squamous cell carcinoma	244 (28.3%)	229 (26.5%)
Large cells	76 (8.8%)	77 (8.9%)
NSCLC, NOS	106 (12.3)	146 (16.9)

Abbreviations: CP, cisplatin/pemetrexed; CG, cisplatin/gemcitabine; NOS, no other specified.

Based on the results of this study, European regulatory approval of pemetrexed in combination with cisplatin has been granted for first-line treatment of patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology.

Differences in the efficacy between non-squamous and squamous patients

A prespecified analysis of the Scagliotti trials[35] showed that patients with non-squamous tumors had significant improvement in overall survival. Patients in the cisplatin/pemetrexed arm with adenocarcinoma and large-cell carcinoma had significantly better survival than patients in cisplatin/gemcitabine arm. Median survival in both arms was 10.28 months, with a hazard ratio of 0.93 and a non-inferiority $p < 0.0001$. However, when comparing by histology type, significant differences were seen between the 2 arms in patients with adenocarcinoma and large cell carcinoma: those with adenocarcinoma who were randomized to cisplatin/pemetrexed had a median survival of 12.55 months vs 10.94 months for those in the cisplatin/gemcitabine arm. In patients with large cell carcinoma, patients randomized to cisplatin/pemetrexed had a median survival of 10.38 months vs 6.67 months for the cisplatin/gemcitabine arm.

In 2003 Sigmond[36] demonstrated that patients with high levels of thymidylate synthase (TS) expression, such as those with squamous carcinoma, are less sensitive to pemetrexed.

In 2006 Ceppi[37] reported that squamous cell and high-grade carcinoma are related to higher TS expression levels, which should be considered when treating patients with TS-inhibiting agent. This unfavorable effect on overall survival associated with squamous cell histology observed with pemetrexed was also noted in a retrospective analysis[38] of the single-agent trial of pemetrexed versus docetaxel in patients with stage III/IV NSCLC after prior chemotherapy.[31] Peterson showed that median overall survival and progression free survival in patients with non-squamous histology cancer treated with pemetrexed was higher than in those with squamous histology (overall survival 9.2 months vs 6.2 months, hazard ratio 0.48, $p < 0.001$; progression free survival 3.4 vs 2.3, hazard ratio 0.56, $p < 0.004$).

A recent review from Hirsch[39] considered the prognostic and predictive role of histology in advanced NSCLC.

The optimal duration of first-line treatment with platinum-based chemotherapy remains unclear. ASCO guidelines recommed that patients with stage IIIB and stage IV receive no more than 4 and 6 cycles[40] because chemotherapy beyond 4 cycles was found to improve progression free survival but not overall survival, and to increase toxicity.[41]

Single-agent maintenance therapy could potentially provide a further increase in overall survival, slow disease progression, and improve quality of life with minimal side effects.

In 2008, Ciuleanu[42] presented the results of a large, randomized phase III pivotal study in which pemetrexed demonstrated an advantage over best supportive care in a postinduction maintenance setting after administration of 1 of 6 commonly prescribed induction regimens: carboplatin/gemcitabine, cisplatin/gemcitabine, carboplatin/docetaxel, cisplatin/docetaxel, carboplatin/paclitaxel, or cisplatin/paclitaxel. All patients received vitamin B12, folic acid and dexamethasone.

Patients treated with pemetrexed in postinduction maintenance therapy had superior progression free survival (4.3 vs 2.6 months; hazard ratio 0.502, 95% confidence interval 0.41–0.61, $p < 0.00001$), especially in the non-squamous histology sub-group.

In the Ciuleanu study[42] progression free survival was no different in the squamous cell patients treated with pemetrexed vs placebo, suggesting that, in patients with squamous cell carcinoma, the benefit with pemetrexed is lower. Patients with squamous cell carcinoma had a median progression free survival of 2.5 months with placebo and a median progression free survival of 2.48 months with pemetrexed.

By contrast, in patients with adenocarcinoma and large cell carcinoma, the benefit in progression free survival was significant. Patients with non-squamous carcinoma had a median progression free survival of 4.37 months with pemetrexed and a median progression free survival of 1.84 months with placebo. The number of large cell patients was small, but the difference was significant in the adenocarcinoma subgroup; in these patients, median progression free survival was 4.60 with pemetrexed and 2.66 months with placebo. There was also a significant benefit in overall survival in the subset of non-squamous patients; preliminary analysis showed a median overall survival of 14.4 months with pemetrexed and 9.4 months with placebo.

There were no significant toxicity differences between arms except for grade 3–4 anemia (pemetrexed 3.9%, placebo 0.9%). Postinduction maintenance therapy with pemetrexed was well tolerated, and confirmed that pemetrexed was more efficacious in patients with non-squamous histology. Pemetrexed is a good candidate for maintenance therapy for

its efficacy, ease of administration and favorable toxicity profile.

Conclusions

Pemetrexed is active against advanced or metastatic NSCLC as both first- and second-line treatment.

It has the potential to play a key role in improving efficacy and toxicity, having demonstrated activity as a single or combination agent, other than predominantly squamous cell histology.

Postinduction maintenance therapy with pemetrexed is being evaluated in a phase III, double-blind, placebo controlled study.

The benefit with maintenance pemetrexed is a real change in the treatment paradigm, because in the past we had not seen any activity of an agent in the maintenance setting. Because pemetrexed can be administered over a prolonged period without cumulative toxicity, it may allow the disease to convert to a "chronic" state.

Disclosures

The authors report no conflicts of interest.

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