Pemetrexed as second-line therapy for advanced non-small-cell lung cancer (NSCLC)

Enriqueta Felip[1]
Rafael Rosell[2]

[1]Vall d'Hebron University Hospital, Barcelona, Spain; [2]Institut Català d'Oncologia, Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain

Abstract: NSCLC accounts for 80% of all cases of lung cancer, which is the leading cause of cancer mortality. The majority of NSCLC patients present with advanced, unresectable disease, which remains incurable. In advanced disease, chemotherapy with platinum (cisplatin or carboplatin) in combination with a third-generation cytotoxic drug (vinorelbine, gemcitabine, paclitaxel, or docetaxel) can provide a modest improvement in survival without impairing quality of life. In chemotherapy-naïve, advanced, non-squamous NSCLC patients, the combination of bevacizumab with chemotherapy was shown to produce better outcomes than chemotherapy alone. Response rates of 20%–40% can now be expected, with a median survival of 8–11 months and a 1-year survival rate of 30%–40%. In second-line treatment, docetaxel has shown superiority to best supportive care in terms of survival and quality of life. A pooled analysis comparing docetaxel administered weekly versus 3-weekly found similar survival rates between the schedules and a non-significant reduction in febrile neutropenia for the weekly regimen. Pemetrexed, a multitargeted antifolate agent, has shown clear activity in several tumors, including mesothelioma and NSCLC. In a phase III trial, second-line treatment with pemetrexed demonstrated overall survival comparable to docetaxel, with a more manageable toxicity profile.

Keywords: pemetrexed, second-line therapy, NSCLC

Pemetrexed is a novel antifolate antimetabolite that targets multiple folate-dependent enzymatic pathways and inhibits multiple enzymes involved in purine and pyrimidine synthesis (Adjei 2004). In preclinical studies pemetrexed has demonstrated antitumor activity in a variety of solid tumor cell lines. Additive or synergic effects were obtained when pemetrexed was combined with other cytotoxic agents, including cisplatin. Pemetrexed has proven clinical activity in non-small-cell lung cancer (NSCLC) patients (Dubey 2005). The contribution of pemetrexed to the treatment of NSCLC patients is analyzed in this review.

Pemetrexed in second-line treatment

In a randomized phase III trial the efficacy and toxicity of pemetrexed was compared to docetaxel in relapsed NSCLC patients (Hanna et al 2004). Until that trial, docetaxel was the only approved cytotoxic chemotherapy for second-line NSCLC treatment. Eligible patients had a performance status of 0 to 2, previous treatment with one prior chemotherapy regimen for advanced disease, and adequate organ function. In this non-inferiority study, both pemetrexed and docetaxel were given on day 1 of a 21-day cycle. Patients in the pemetrexed arm received folate and B12 supplementation. Five hundred and seventy-one eligible patients were randomized to receive either pemetrexed or docetaxel. Pre-randomization stratification factors included performance status, disease stage, number of previous chemotherapy regimens, response to most

Correspondence: Rafael Rosell
Institut Català d'Oncologia, Hospital Germans Trias I Pujol, Ctra. Canyet. s/n, 08916 Badalona, Barcelona, Spain
Tel +34 93 497 8925
Fax +34 93 4978950
Email rrosell@ico.scs.es

recent chemotherapy, whether the patient had ever received either platinum, or paclitaxel therapy, treatment site, and baseline homocysteine level. Following disease progression, post-study chemotherapy was allowed. The results of this study are summarized in Table 1. Response rates were 9.1% and 8.8%, and median survival times were 8.3 months and 7.9 months in the pemetrexed and docetaxel arms, respectively. Median progression-free survival was 2.9 months for each arm and the 1-year survival rate for each arm was 29.7%. The docetaxel arm had higher incidence of grade 3/4 neutropenia (40% vs 5%), neutropenic fever (13% vs 2%), and neuropathy (8% vs 3%) than the pemetrexed arm. Thus, pemetrexed produced similar results and was better tolerated than docetaxel in the treatment of pretreated NSCLC patients (Cohen 2005).

Weiss et al performed a subset analysis of the above randomized phase III trial of pemetrexed vs docetaxel to analyze whether the elderly population benefits from second-line cytotoxic chemotherapy (Weiss et al 2006). Eighty-six of 571 patients (15%) were ≥70 years old, similar to rates of elderly observed in the first-line setting. Elderly patients receiving pemetrexed (n = 47) or docetaxel (n = 39) had a median survival of 9.5 months and 7.7 months compared with 7.8 months and 8.0 months for younger patients receiving pemetrexed (n = 236) or docetaxel (n = 249), respectively. Elderly patients treated with pemetrexed had a longer time to progression and a longer survival than their counterparts treated with docetaxel (not statistically significant). Febrile neutropenia was less frequent in the elderly patients treated with pemetrexed (2.5%) than in those receiving docetaxel (19%; $p = 0.025$).

Pujol et al performed a retrospective risk-benefit analysis of survival without grade 3–4 toxicity, defined as the time to the first occurrence of Common Toxicity Criteria grade 3 or 4 toxicity or death, in the above prospective phase III study comparing pemetrexed with docetaxel (Pujol et al 2007). In this analysis, pemetrexed demonstrated a statistically significant longer survival without grade 3/4 toxicity compared with docetaxel (HR 0.60; $p < 0.0001$). A supportive analysis based on selected grade 3/4 toxicities (neutropenia lasting >5 days, febrile neutropenia, infection with neutropenia, anemia, thrombocytopenia, fatigue, nausea, vomiting, diarrhea, stomatitis, and neurosensory events) also demonstrated an advantage for pemetrexed (HR 0.53; $p < 0.0001$). This analysis of survival without grade 3/4 toxicities suggests a benefit-to-risk profile that favors pemetrexed over decetaxel in the second-line treatment of NSCLC patients.

Table 1 Efficacy results of the phase III second-line trial comparing pemetrexed with docetaxel

	Pemetrexed N = 283	Docetaxel N = 288	HR; p value
Median overall survival	8.3 months	7.9 months	HR = 0.99 P 0.93
1-year survival rate	29.7%	29.7%	–
Median progression-free survival	2.9 months	2.9 months	–
Time to progressive-disease	3.4 months	3.5 months	–
Overall response rate	9.1%	8.8%	–

In another subset analysis, the investigators evaluated the impact of first-line chemotherapy on the outcome of second-line chemotherapy (Weiss et al 2007a). Comparisons were made based on type of first-line chemotherapy (gemcitabine/platinum, taxane/platinum, or others), response to initial therapy, and clinical characteristics. By multivariate analysis, gender, stage at diagnosis, performance status, and best response to first-line therapy significantly influenced overall survival.

The activity and toxicity of pemetrexed has been evaluated in a post-registration study in routine clinical practice (Bearz et al 2007). One hundred and sixty patients from 4 different Italian institutions, treated with pemetrexed, mostly as second-line therapy, were analyzed. There was a predominance of males, adenocarcinoma, and the median age was 63.6 years. Toxicity was mild, the response rate was 11.2%, and median survival was 12 months.

During the 2007 ASCO meeting, Cullen et al presented a study in which they compared a high dose of pemetrexed (900 mg/m^2) with the standard dose (500 mg/m^2), each given once every 21 days, in advanced NSCLC patients with disease progression after treatment with a platinum-containing regimen (Cullen et al 2007). The primary objective of this study was survival. In this trial, 629 patients were accrued, of which 588 were eligible for inclusion, 295 received the standard pemetrexed dose and 293 received the higher pemetrexed dose. No differences were detected between the high dose and the standard dose of pemetrexed in terms of survival, progression-free survival or response rate. Overall survival in the two arms was equivalent (median survival of standard dose of 6.7 months compared with 6.9 months for patients who received the higher dose). The efficacy results of this study are summarized in Table 2. Patients in the higher dose arm had slightly higher toxicity. In a similar Japanese study, 244 patients with prior chemotherapy were randomized to

Table 2 Pemetrexed 500 mg/m^2 vs 900 mg/m^2 in second-line NSCLC treatment – efficacy results

	Pemetrexed 500 mg/m^2 N = 295	Pemetrexed 900 mg/m^2 N = 293	Statistical values
Median survival	6.7 months	6.9 months	HR = 1.01
Progression-free survival	2.6 months	2.8 months	HR = 0.97
Overall response rate	7.1%	4.3%	P = 0.1616

receive pemetrexed 500 mg/m^2 or pemetrexed 1000 mg/m^2 (Ichinose et al 2007). Overall response rate was 18% for the standard pemetrexed dose and 15% for the high pemetrexed dose. Median progression-free survival was 3.0 months for the standard pemetrexed dose and 2.4 months for the high pemetrexed dose. Thus, the standard pemetrexed dose in second-line therapy should remain at 500 mg/m^2.

Pemetrexed in combination in NSCLC

The combination of pemetrexed/carboplatin has been analyzed in several trials. In the study of Zinner et al 55 patients received carboplatin (AUC = 6) and pemetrexed 500 mg/m^2 day 1 every 3 weeks (Zinner et al 2005). The response rate was 24%, median time to progression was 5.4 months, 1-year survival 56%, and median survival 13.5 months. This was a very well-tolerated regimen. Pemetrexed and gemcitabine have demonstrated independent anti-tumor activity in patients with advanced NSCLC. In a phase II study, 53 chemotherapy-naïve advanced NSCLC patients received pemetrexed immediately after gemcitabine in day 1 (Treat et al 2006). Best tumor response consisted of 1 patient with complete response (2.0%), 15 with partial response (30.6%), 17 with stable disease (34.7%), and 16 with progressive disease (32.7%). Median time to disease progression was 3.3 months and median survival was 10.3 months.

In a phase I/II study of pemetrexed/vinorelbine in combination, the authors investigated the usefulness of plasma pharmacokinetic and pharmacodynamic measures in understanding the time course and extent of the inhibition of thymidylate synthase by pemetrexed (Li et al 2007). Eighteen patients received folic acid and vitamin B12 supplements 1 week before beginning pemetrexed/vinorelbine treatment. Blood samples were collected in the first cycle for pharmacokinetic analyses and in the first two cycles for determination of plasma thymidine, deoxyuridine, homocysteine and methylmalonic acid concentrations. The results of this study suggest that the thymidylate synthase inhibitory effects of pemetrexed are short-lived and make the case for a more frequent schedule of administration, such as every 2 weeks. Baseline homocysteine concentration remains a predictive marker for hematologic toxicity even following folate supplementation.

Pemetrexed has also been combined with bevacizumab. In a multicenter phase II study the researchers evaluated the safety of combining bevacizumab with either chemotherapy (pemetrexed or docetaxel) or erlotinib (Herbst et al 2007). One hundred and twenty patients were randomly assigned and treated. The risk of disease progression or death was 0.66 among patients treated with bevacizumab/chemotherapy and 0.72 among patients treated with bevacizumab/erlotinib when compared to those treated with chemotherapy alone, although the differences were not statistically significant. One-year survival rate was 57.4% for bevacizumab/erlotinib and 53.8% for bevacizumab/chemotherapy compared with 33.1% for chemotherapy alone. The conclusion of this study was that progression-free survival favored bevacizumab in combination with either chemotherapy or erlotinib over chemotherapy alone in the second-line setting. No unexpected toxicities were noted.

In a single-institution experience, patients with advanced NSCLC with progression following first-line therapy and who received either pemetrexed alone or pemetrexed/bevacizumab were analyzed (Weiss et al 2007b). Twenty-five patients were treated with pemetrexed or pemetrexed/bevacizumab. After a median follow-up of 9.3 months, no differences were observed between the cohorts for median overall survival, time to progression, or disease control rate. There were no grade 3–5 hemorrhagic events. In this retrospective single institution analysis, the authors concluded that pemetrexed/bevacizumab was safely administered in the salvage setting of advanced disease. Whether bevacizumab enhances the efficacy of pemetrexed remains to be determined and is the subject of an ongoing randomized clinical trial.

The combination of pemetrexed with other targeted agents has been tested in NSCLC clinical trials. Pemetrexed/vandetanib (ZD6474) combination has been analyzed in a phase I trial in previously treated NSCLC patients (De Boer et al 2007). Pemetrexed/vandetanib was generally well tolerated, with no apparent PK interaction. In 18 patients evaluable for efficacy, one had partial response and 13 patients had stable disease. A phase III trial of pemetrexed/vandetanib 100 mg in second-line NSCLC has begun.

A phase I-IIa study evaluated the feasibility of combining pemetrexed/cetuximab in patients with recurrent NSCLC (Jalal et al 2007). In this study it was found feasible and safe to combine pemetrexed at 750 mg/m^2 every 21 days and cetuximab at 400 mg/m^2 week 1 and 250 mg/m^2 weekly thereafter. Response data were available for 18 patients, with partial response in 2 patients (9%) and stable disease in 8 patients (35%).

Pemetrexed in first-line treatment of advanced NSCLC

In a multicenter phase II trial, the investigators determined the efficacy and toxicity of two pemetrexed-based regimens in chemotherapy-naïve patients with advanced NSCLC (Scagliotti et al 2005a). Forty-one patients received pemetrexed/oxaliplatin and 39 received pemetrexed/carboplatin. Objective response rates were 26.8% for pemetrexed/oxaliplatin patients and 31.6% for pemetrexed/carboplatin patients. Median time to progression was 5.5 and 5.7 months for pemetrexed/oxaliplatin and pemetrexed/carboplatin, respectively. Median overall survival was 10.5 months for both treatment groups. The 1-year survival rate was 49.9% for pemetrexed/oxaliplatin patients and 43.9% for pemetrexed/carboplatin. Hematologic toxicities among pemetrexed/oxaliplatin-treated patients were grade 3/4 neutropenia (7.3%), grade 3 thrombocytopenia (2.4%), and grade 3 anemia (7.3%). Pemetrexed/carboplatin-treated patients experienced grade 3/4 neutropenia (25.6%), grade 3/4 thrombocytopenia (17.9%), and grade 3 anemia (7.7%). Three patients had febrile neutropenia (pemetrexed/oxaliplatin 1 and pemetrexed/carboplatin 2).

In a randomized phase II trial single agent pemetrexed or sequential pemetrexed/gemcitabine was evaluated in chemotherapy-naïve patients with NSCLC who were elderly (≥70 years) or younger than 70 years and ineligible for platinum-based chemotherapy (Gridelli et al 2007). Eighty-seven patients received treatment (44 pemetrexed; 43 pemetrexed/gemcitabine). The median time to progression was 4.5 and 4.1 months for the pemetrexed and pemetrexed/gemcitabine arms, respectively, and the median progression-free survival time was 3.3 months for both arms. Tumor response rates for the pemetrexed and pemetrexed/gemcitabine arms were 4.5% and 11.6%, respectively. The median overall survival time was 4.7 months for the pemetrexed arm and 5.4 months for the pemetrexed/gemcitabine arm, with respective 1-year survival rates of 28.5% and 28.1%. Grade 3/4 hematologic toxicity consisted of neutropenia (4.5% pemetrexed; 4.7% pemetrexed/gemcitabine), thrombocytopenia (4.5% pemetrexed; 7.0% pemetrexed/gemcitabine), and anemia (6.8% pemetrexed; 4.7% pemetrexed/gemcitabine). No grade 3/4 nonhematologic toxicities exceeded 4.7% in either arm. The conclusion of this phase II trial is that single-agent pemetrexed and sequential pemetrexed/gemcitabine have shown moderate activity and are well tolerated as first-line treatment for advanced NSCLC in elderly patients or those deemed unsuitable for platinum-based combination chemotherapy.

During the ASCO 2007 meeting, the Norwegian Lung Cancer Group presented a phase III trial comparing pemetrexed (500 mg/m^2 on day 1) or gemcitabine (1000 mg/m^2 on days 1 and 8) in combination with carboplatin (AUC = 5 on day 1) as first-line therapy for patients with advanced NSCLC (Gronberg et al 2007). Each regimen was administered every 3 weeks. A total of 446 patients were included; 219 received pemetrexed/carboplatin and 218 gemcitabine/carboplatin. Mean quality of life scores were stable throughout the study period, and no significant differences were noted between the treatment arms. However, there were significant differences in toxicity, with patients in the gemcitabine arm experiencing more grade 3 and 4 leukopenia and thrombocytopenia. There was no difference in overall survival for patients in the two arms; median survival for patients receiving pemetrexed was 7.3 months compared with 7.0 months for patients receiving gemcitabine.

During the 12th World Conference on Lung Cancer, Scagliotti et al presented the results of a phase III study of pemetrexed/cisplatin vs gemcitabine/cisplatin in chemotherapy-naïve patients with locally advanced or metastatic NSCLC (Scagliotti et al 2007b). ECOG PS 0–1 patients were randomized to receive cisplatin 75 mg/m^2 day 1 with pemetrexed 500 mg/m^2 day 1 or gemcitabine 1250 mg/m^2 day 1, 8 with cisplatin 75 mg/m^2 day 1, every 3 weeks. Both arms received folic acid, vitamin B12, and dexamethasone. The primary endpoint of this non-inferiority study was overall survival. From July 2004 to December 2005, 1725 patients were randomized. Overall survival for patients randomized to pemetrexed/cisplatin was non-inferior to gemcitabine/cisplatin (10.3 vs 10.3 months; HR = 0.94). Similarly, progression-free survival and response rate showed non-inferiority for pemetrexed/cisplatin vs gemcitabine/cisplatin. Hematologic grade 3/4 toxicities were statistically significantly lower for pemetrexed/cisplatin. Less grade 3/4 nausea and anorexia were observed for gemcitabine/cisplatin. In a pre-specified analysis by histologic groups, pemetrexed/cisplatin had significantly better survival than gemcitabine/cisplatin in the adenocarcinoma

group (N = 847; 12.6 vs 10.9 months; HR = 0.84) and in large cell histology (N = 153; 10.4 vs 6.7 months; HR = 0.68). In contrast, there was a non-significant trend toward better survival with gemcitabine/cisplatin in squamous cell histology (N = 473; 9.4 vs 10.8 months; HR = 1.22).

Pemetrexed in combination with thoracic radiotherapy in unresectable stage III NSCLC

In a phase I trial, the maximum tolerated dose for pemetrexed alone and in combination with carboplatin plus concurrent radiotherapy was determined (Seiwert et al 2007). Patients with advanced NSCLC or esophageal cancer were given two cycles with a 21-day interval. Patients received either pemetrexed or pemetrexed/carboplatin, both with concurrent radiation. In this study the combination of pemetrexed (500 mg/m^2) and carboplatin (AUC = 5 or 6) with concurrent radiation was well tolerated, allowed for the administration of systemically active chemotherapy doses and showed signs of activity. A phase I study of concurrent pemetrexed/cisplatin and concurrent thoracic radiotherapy (61–66 Gy) in unresectable stage IIIA/B patients has been recently carried out (Brade et al 2007). In this study, full dose pemetrexed and cisplatin given concurrently with full dose radiotherapy was well tolerated and a phase II study is planned.

Pemetrexed in early-stage NSCLC

About 30% of NSCLC patients are diagnosed with early-stage of disease. Adjuvant chemotherapy has been proven to be beneficial for certain patients with resected NSCLC. The majority of patients in the adjuvant treatment setting receive a combination of cisplatin/vinorelbine. However, toxicity and insufficient dose delivery have been critical issues. The combination of cisplatin/vinorelbine has resulted in rates of grade 3/4 neutropenia of around 75% and rates of febrile neutropenia of up to 12%. In the TREAT phase II study ("Trial of Refinement of Early stage NSCLC. Adjuvant chemotherapy with pemetrexed and cisplatin vs vinorelbine and cisplatin"), patients with pathologically stage IB, II, T3N1, and complete surgical resection are randomized to receive either 4 cycles of adjuvant vinorelbine/cisplatin, or 4 cycles of pemetrexed 500 mg/m^2 day 1 and cisplatin 75 mg/m^2 day 1 every 3 weeks (Kreuter et al 2007). The primary objective is to compare clinical feasibility of these cisplatin doublets defined as non-occurrence of grade 4 neutropenia and/or thrombocytopenia for $>$7 days or bleeding, grade 3/4 febrile neutropenia and/or infection, grade 3/4 non-hematological toxicity, non-acceptance leading to premature withdrawal, and no cancer or therapy-related death. Secondary parameters are efficacy (time to relapse, overall survival) and drug delivery. The hypothesis of the study is that reduced toxicity will improve the feasibility of drug delivery, compliance, and the convenience of treatment for the patients. In this study a total of 134 patients are planned.

Pharmacogenomic assessment

A crucial aspect of the clinical development of new drugs is to understand which patients will reap clinical benefit from their use (Rosell et al 2004a). The clinical application of mRNA expression levels of amplified genes may disclose extensive genetic impact on cytotoxic drug sensitivity and enable clinicians to tailor chemotherapy to each individual's genetic profile. The assessment of thymidilate synthase mRNA expression levels might prove useful to select patients who will benefit from pemetrexed (Rosell et al 2004b).

Scagliotti et al quantified mRNA and protein levels in pretreatment biopsies of patients included in the previously mentioned phase III trial comparing pemetrexed/cisplatin with gemcitabine/cisplatin in order to identify biomarkers that may predict clinical outcome (Scagliotti et al 2007c). Of 232 patients with tissue samples, 69 had gene expression results and 181 had immunohistochemistry results. High EGFR expression was associated with improved clinical outcome irrespective of treatment arm; high EGFR was associated with improved progression-free survival and time to progression regardless of treatment arm. A statistically significant interaction between thymidylate synthase and treatment effect was observed for time to disease progression. The results of this subset analysis suggest a potential association between low thymidylate synthase expression and improved outcome with pemetrexed/cisplatin.

In a retrospective analysis of the phase III study comparing pemetrexed versus docetaxel in second-line setting, the authors presented the finding that docetaxel had statistically better survival than pemetrexed in the squamous cell subgroup, while pemetrexed had statistically better survival than docetaxel in the combined non-squamous subgroup (Peterson et al 2007). These results agree with those reported in the first-line study comparing cisplatin/gemcitabine with cisplatin/pemetrexed mentioned earlier. A further study indicated higher thymidylate synthase expression in squamous cell carcinoma than in adenocarcinoma. One hypothesis is that thymidylate synthase overexpression in squamous cell

carcinoma leads to reduce pemetrexed sensitivity. Larger translational research studies to determine the prognostic and predictive value of biomarkers in pemetrexed-treated patients are required.

Hsu et al used a genomic strategy to develop signatures predictive of chemotherapeutic response to both cisplatin and pemetrexed (Hsu et al 2007). Using in vitro drug sensitivity data, coupled with microarray data, the investigators developed gene expression signatures predicting sensitivity to cisplatin and pemetrexed. Signatures were validated with response data from 32 independent ovarian and lung cancer cell lines as well as 59 samples from patients previously treated with cisplatin. In this experience, genomic-derived signatures of cisplatin and pemetrexed sensitivity were shown to accurately predict sensitivity in vitro and, in the case of cisplatin, to predict treatment response in patients treated with cisplatin. Interestingly, an inverse correlation was seen between in vitro cisplatin and pemetrexed sensitivity, and between the likelihood of cisplatin and pemetrexed response in patients. The conclusion of the authors is that the use of genomic predictors of response to cisplatin and pemetrexed can be incorporated into strategies to optimize therapy in advanced solid tumors.

Summary

Pemetrexed is a novel antimetabolite with inhibitory activity against a number of folate-dependent enzymes. As second-line treatment for advanced NSCLC, pemetrexed, when administered with folic acid and vitamin B12, has demonstrated comparable efficacy and a better toxicity profile relative to docetaxel. In first-line treatment pemetrexed in combination with cisplatin produces equivalent response and overall survival compared to a combination of cisplatin/gemcitabine. The role of targeted agents in combination with pemetrexed as well as pharmacogenomic approaches is, at present, being evaluated in NSCLC patients.

Disclosures

Neither author has any conflicts of interest to declare.

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