

Maintenance therapy for metastatic non-small-cell lung cancer – the role of pemetrexed

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Abstract: Over the last several years, we have greatly enhanced our understanding of tumor biology and have now integrated novel and molecular-targeted therapies into front-line treatment for locally advanced and metastatic non-small-cell lung cancer (NSCLC). Despite all the recent advances, the improvement in survival outcomes for these patients has been measured in weeks compared to historical controls. Clinical researchers continue to search for the silver bullet that will allow oncologists to treat lung cancer as a chronic illness and prolong life well beyond the statistical barrier of 1 year for these patients. In that vein, maintenance therapy is emerging as a new treatment option in the metastatic setting. However, there is much controversy over the validity and cost-effectiveness of this modality. Recently, a phase III trial of pemetrexed maintenance versus best supportive care in the setting of metastatic NSCLC following non-progression after 4 cycles of platinum-based doublet therapy showed significant survival outcomes of the treatment group. This article will review the current available treatment options in metastatic NSCLC, including maintenance regimens, with particular attention paid to the recent pemetrexed study.

Keywords: non-small-cell lung cancer, pemetrexed, maintenance therapy

Introduction

The number of newly diagnosed cases of cancer nationwide approached 1.5 million in 2009.¹ Lung cancer will account for more than 10% of these new cases, numbering almost 220,000,¹ more than any other single organ site. Non-small-cell lung cancer (NSCLC) comprises about 85% of all cases.¹ 160,000 people are expected to die in 2010 from lung cancer, making it the leading cause of cancer death in North America.¹ Mortality from all cancers has trended downward gradually, but consistently, since 1993.² However, the reduction in the number of deaths from lung cancer has been modest at best due to a variety of factors, including a plateau in the reduction of female lung cancer deaths, but mainly due to the high mortality rate of patients with metastatic disease.^{3,4} One of the major challenges in reducing the mortality associated with NSCLC is the fact that more than 50% of patients present with metastatic disease at the time of diagnosis.^{4,5} The prognosis in this subset of patients with stage IIIB (with malignant pleural or pericardial effusion) or stage IV disease, remains poor. The revised TNM staging for lung cancer will incorporate these patients into stage IV disease as of January 1, 2010 and will classify them as M1a disease based on their inferior median survival compared to patients with T4 disease (8 months versus 13 months).⁵ With a median survival of less than 1 year and a 5-year survival in this population of 3.5%,⁴ efforts continue at an ever-increasing pace to try and improve this outcome.

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This decade has seen a proliferation of single-agent and combination regimens in treating metastatic NSCLC, as well as the advent of molecular targeted therapies. One of the chemotherapeutic agents approved for treating metastatic NSCLC is pemetrexed, a novel multitargeted antifolate.⁶ This review will focus on the treatment of metastatic NSCLC, highlighting several landmark trials, including the expanding role of pemetrexed and the emerging data regarding its potential use as maintenance therapy.

First-line therapy for metastatic disease

A number of agents are currently approved for first-line therapy in stage IIIB or stage IV NSCLC in patients with an ECOG performance status of 0 to 1. Research dating back more than 20 years first established the concept of platinum-based chemotherapy being superior in overall survival compared to best supportive care (BSC). Rapp et al in 1988 compared platinum-based chemotherapy in advanced NSCLC versus best supportive care in one of the earliest lung cancer trials with a relatively robust sample size.⁷ A meta-analysis published by the Non-small Cell Lung Cancer Collaborative Group in 1995 provided more evidence for the potential survival benefit of chemotherapy versus BSC in treating NSCLC.⁸ The ECOG 1594 trial, published by Schiller et al in 2002, confirmed platinum doublet regimens as the standard in first-line therapy for advanced disease.⁹ The trial demonstrated equivalent outcomes in response rates and overall survival comparing cisplatin and paclitaxel with 3 different platinum-based chemotherapy regimens: cisplatin and gemcitabine; cisplatin and docetaxel; or carboplatin and paclitaxel. A pivotal phase III trial published by Scagliotti et al in 2008, originally designed as a non-inferiority trial, compared cisplatin–gemcitabine, a standard first-line regimen for advanced NSCLC, with cisplatin–pemetrexed.¹⁰ Overall survival for cisplatin–pemetrexed was noninferior to cisplatin–gemcitabine and a median survival of 10.3 months was achieved in both arms. Overall survival was statistically superior for cisplatin–pemetrexed versus cisplatin–gemcitabine in patients with adenocarcinoma ($n = 847$; 12.6 vs 10.9 months, respectively) and large-cell carcinoma histology ($n = 153$; 10.4 vs 6.7 months, respectively). However, in patients with squamous cell histology, cisplatin–gemcitabine demonstrated a significant survival benefit versus cisplatin–pemetrexed ($n = 473$; 10.8 vs 9.4 months, respectively). Already approved as a second-line single-agent therapy in advanced or recurrent NSCLC, pemetrexed was subsequently approved as a first-line agent

in combination with cisplatin in NSCLC, non-squamous cell histology. Interestingly, this trial was the first to demonstrate differential efficacy in NSCLC based on tumor histology, presumably due to increased levels of thymidylate synthase in squamous cell tumors.¹¹

The addition of targeted therapies to established chemotherapy doublets expanded the arsenal of agents in advanced NSCLC to improve overall survival in select patients who meet specific eligibility criteria. Sandler et al in 2006 demonstrated the success of adding the vascular endothelial growth factor (VEGF) receptor inhibitor bevacizumab to carboplatin–paclitaxel in a phase III trial, ECOG 4599.^{12,13} Superior outcomes were seen in response rates, progression-free survival and overall survival, with an increase in overall survival of 2 months for carboplatin–paclitaxel–bevacizumab versus carboplatin–paclitaxel alone (12.3 vs 10.3 months, respectively). Survival benefits, however, came at a cost of statistically significant increase in toxicities and treatment-related deaths. Five deaths were attributed to pulmonary hemorrhage, 5 to complications of febrile neutropenia, 2 each to a cerebrovascular event or gastrointestinal hemorrhage, and 1 to a probable pulmonary embolus. The majority of treatment-related deaths occurred within the first 2 cycles of therapy. The FLEX trial results, published in abstract form by Pirker et al in 2008, added the epidermal growth factor receptor (EGFR) inhibitor cetuximab to the doublet of cisplatin and vinorelbine.¹⁴ The survival benefit of the group receiving chemotherapy plus cetuximab was irrespective of tumor histology. This regimen is the only combination chemotherapy approved for patients with an ECOG performance status of 2.

Second-line therapy for metastatic disease

Several studies have shown the benefits of single-agent chemotherapy in the second-line setting. Combination regimens have proven too toxic in the second-line setting, sometimes with inferior survival compared to single agents.¹⁵ Currently, 3 drugs are approved for single-agent therapy in metastatic NSCLC in patients with an ECOG performance status of 0 to 2. The TAX 317¹⁶ and TAX 320¹⁷ trials in 2000 compared docetaxel with BSC and with vinorelbine or ifosfamide, respectively. Both trials demonstrated superior overall survival with single-agent docetaxel as well as improved quality of life in the docetaxel arms. Pemetrexed was approved for second-line therapy after Hanna et al in 2004 found it to be equivalent to docetaxel in terms of response rates, progression-free survival and overall survival.¹⁸ Additionally,

pemetrexed therapy had a better toxicity profile, most notably a statistically significant decrease in hospitalization rates for neutropenic fever compared to docetaxel. The EGFR inhibitor erlotinib was approved in late 2004 after it proved superior to placebo in prolonging median overall survival by 2 months.¹⁹ Response to erlotinib was significantly higher in non-smokers, the presence of adenocarcinoma and EGFR expression. Other subgroups in the study that did not demonstrate these characteristics still did exhibit some response to erlotinib though. Of the 731 patients enrolled in the study, 50% of them had received 2 or more chemotherapy regimens. The response rate and survival benefit in this group was identical to patients who had been treated with only 1 prior regimen. Based on these results, erlotinib was approved for third-line treatment and remains the only agent in this category. A recent Korean trial published in 2008 also evaluated pemetrexed as a third-line agent, with encouraging results.²⁰

A question of timing

Throughout the past decade, research has sought to address the issue of determining the appropriate length of time to administer chemotherapy. Studies have consistently shown that a short, fixed number of 3 to 4 cycles in the first-line setting provided the greatest balance of overall survival benefit with acceptable levels of toxicity.^{21,22} Treating beyond 4 cycles of first-line chemotherapy has generally increased toxicity and may decrease the likelihood of patients ever receiving second-line agents. Park et al conducted a trial that supports this theory. In 2007, the Korean Cancer Study Group randomly assigned 314 patients with stages IIIB or IV NSCLC who had not progressed after 2 cycles of chemotherapy to receive either 2 or 4 additional cycles of cisplatin-based chemotherapy.²³ No survival benefit was noted in the group receiving 4 additional cycles. However, 99 (62.7%) of 158 patients in the 4-cycle arm and 116 (74.4%) of 156 patients in the 2-cycle arm received second-line chemotherapy, and these values were significantly different ($P = 0.026$). Patients in the 2-cycle arm also had a significantly less toxicity and better recovery of role function compared to the 4-cycle arm.

Only 1 trial demonstrated a survival benefit when continuing first-line platinum-based chemotherapy beyond 4 cycles. Barata et al conducted a trial comparing 4 versus 6 cycles of carboplatin and gemcitabine in patients with stage IIIB or IV NSCLC.²⁴ The time to progression was not significantly different between the 2 arms, but overall survival was significantly longer on the 6-cycle arm compared with the 4-cycle arm ($P = 0.047$). The median survival on the 4- and 6-cycle treatment arms were 7 months (95% confidence

interval [CI], 5.9–8.1 months) and 12 months (95% CI, 9.8–14.2 months), respectively. Overall survival, though noted to be superior on the 6-cycle arm, was not reported in the abstract. Also, the sample size of 220 patients in this trial may not have been adequate to make a definitive statement about the benefits of extending treatment beyond 4 cycles.

Continuing chemotherapy beyond a fixed number of cycles has also been examined in the second-line setting. Specifically, the options include: waiting until disease progression before initiating second-line therapy, which is the standard approach; switching to a second-line regimen after a fixed number of cycles of first-line chemotherapy; or, continuing first-line therapy until disease progression, then switching to a second-line agent.²¹ While many studies have touted improvements in progression-free survival in a variety of dosing schedules, none have shown a statistically significant benefit in overall survival when compared to first- or second-line regimens given in standard fashion. More recent investigations have reinforced this fact. The trial conducted by Fidias et al in 2009 compared immediate with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced NSCLC.²⁵ Although the trial did show a statistically significant increase in progression-free survival, overall survival was not impacted. What is notable in this study is that patients who actually received the docetaxel in the delayed docetaxel arm in had an identical overall survival of 12.5 months compared to patients in the immediate docetaxel arm. This subset analysis raises an interesting question that other authors have also asked: does the timing of the second-line chemotherapy administration matter, or is it simply the exposure of these patients to the second-line regimen that confers a survival benefit?^{26,27} Further exploration of this hypothesis with appropriately designed trials comparing immediate versus delayed second-line chemotherapy should provide a definitive answer.

Maintenance therapy

A great deal of excitement and controversy has surrounded recent trials testing the concept of maintenance therapy. Since 2001, numerous trials have evaluated the potential role of maintenance therapy in advanced NSCLC with standard chemotherapy and with the newer targeted agents. None of these trials have demonstrated a benefit in overall survival compared to administering second-line therapy at the time of disease progression (Table 1).^{28–35} Overall survival data from the ATLAS trial conducted by Miller et al looking at maintenance bevacizumab with or without erlotinib, is not yet

mature.³⁶ Overall survival results from the SATURN trial conducted by Cappuzzo et al examining the role of maintenance erlotinib versus placebo were recently reported.^{37–39} An overall survival benefit of one month (12 vs 11 months, $P = 0.0088$) was described, favoring erlotinib over placebo.³⁹ However, these data have not yielded any change in clinical practice as of yet, and the issue of maintenance therapy conferring the survival benefit versus the exposure to chemotherapy has not been answered. Currently, 4 to 6 cycles of first-line chemotherapy followed by second-line chemotherapy begun at the time of disease progression remains the preferred method of administration in recurrent or metastatic NSCLC.⁴⁰

Until recently, no trials have examined pemetrexed as maintenance therapy. Given the efficacy, tolerability and ease of administration, it seemed a logical choice for evaluation as a maintenance regimen. Ciuleanu et al published results of their phase III trial data in late 2009 to test this idea.⁴¹ In this randomized, double-blind, placebo-controlled trial, 663 patients with stage IIIB or IV NSCLC who had not progressed on 4 cycles of platinum-based chemotherapy were randomly assigned in a 2:1 ratio to receive pemetrexed in 21-day cycles plus BSC or placebo plus BSC. Treatment was continued until disease progression. Pemetrexed-containing regimens were not included in the initial platinum doublet options since the study began prior to the trial conducted by Scagliotti et al that led to pemetrexed approval for first-line therapy.¹⁰ The

primary endpoint of this study was progression-free survival. Secondary endpoints included overall survival, objective tumor response rate and safety. The results demonstrated superior progression-free survival in the pemetrexed plus BSC arm compared with placebo plus BSC (4.3 months [95% CI 4.1–4.7] vs 2.6 months [1.7–2.8]; hazard ratio [HR] 0.50, 95% CI 0.42–0.61, $P < 0.0001$). The secondary endpoint of overall survival also showed pemetrexed plus BSC to be superior to placebo plus BSC (13.4 months [11.9–15.9] vs 10.6 months [8.7–12.0]; HR 0.79, 0.65–0.95, $P = 0.012$). These outcomes were significant in the non-squamous histology groups. As proven in prior studies, patients with squamous histology did not derive significant benefit from treatment with pemetrexed.^{10,42} Of note, 41 patients (18%) in the placebo arm who were unmasked to study treatment at the time of disease progression went on to receive treatment with pemetrexed, at the discretion of the investigator. No survival data were collected on the post-discontinuation patients who went on to receive further treatment, which would be of potential value in comparing this standard treatment approach to maintenance therapy. Based on the results of this trial and the ongoing debate about maintenance therapy in general, recent updates to the NCCN guidelines now include the options of continuing first-line therapy until disease progression or using pemetrexed as maintenance therapy in non-squamous histology until disease progression.⁴⁰ However, these guidelines are all level

Table I Survival data of previous maintenance chemotherapy trials in advanced NSCLC

| Authors | Number of patients randomized | TTP/PFS | Median overall survival |
|---------------------------------|---|---|-------------------------------------|
| Socinski et al ²⁸ | n = 230 (4 cycles carboplatin-paclitaxel vs continuous treatment until progression) | N/A | 6.6 vs 8.5 mos; $P = 0.63$ |
| Belani et al ²⁹ | n = 130 (paclitaxel vs BSC) | TTP: 38 vs 29 wks; $P = 0.124$ | 75 vs 60 wks; $P = 0.243$ |
| Giaccone et al ³⁰ | n = 1093 (gefitinib maintenance 500 mg/d vs 250 mg/d vs placebo) | TTP: 5.5 vs 5.8 vs 6 mos; $P = 0.7633$ | 9.9 vs 9.9 vs 10.9 mos; $P = 0.456$ |
| Westeel et al ³¹ | n = 181 (maintenance vinorelbine vs observation) | PFS: 5 vs 3 mos; $P = 0.32$ | 12.3 mos in both groups; $P = 0.48$ |
| Brodowicz et al ³² | n = 206 (gemcitabine maintenance vs BSC) | TTP: 3.6 vs 2 mos; $P < 0.001$ | 10.2 vs 8.1 mos; $P = 0.195$ |
| Gatzemeier et al ³³ | n = 1172 (erlotinib vs placebo) | TTP: 23.7 vs 24.6 wks; $P = 0.74$ | 43 vs 44.1 wks; $P = 0.49$ |
| Kelly et al ³⁴ | n = 243 (gefitinib vs placebo) | PFS: 8.3 vs 11.7; $P = 0.17$ | 23 vs 35 mos; $P = 0.013$ |
| Johnson et al ³⁵ | n = 186 (CAI vs placebo) | TTP: 2.8 vs 2.4 mos; $P = 0.5$ | 11.4 vs 10.5 mos; $P = 0.54$ |
| Miller et al ³⁶ | n = 768 (bevacizumab with or without erlotinib) | PFS: 4.8 vs 3.7 mos; $P = 0.0012$ | Data not yet mature |
| Cappuzzo et al ^{37–39} | n = 889 (erlotinib vs placebo) | PFS: HR = 0.71 [95% CI 0.62–0.82]; $P = 0.000003$ | 12 vs 11 mos; $P = 0.0088$ |

Abbreviations: CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; TTP, time to progression.

2B recommendations, indicating a lack of uniform consensus opinion on this issue.

Future directions in pemetrexed therapy

In addition to its possible role in maintenance therapy, efforts continue to define how best to apply pemetrexed in treating advanced or metastatic NSCLC based on its novel mechanism as a multitargeted antifolate and its associated pharmacogenomic profile.⁶ Its potent inhibition of thymidylate synthase has been a focus of clinical trials that examined its role in predicting response to pemetrexed. Bepler et al conducted a trial of 52 patients with resectable NSCLC treated with neoadjuvant gemcitabine and pemetrexed.⁴³ They evaluated the associated levels of gene expression responsible for metabolism of the respective agents to determine whether or not the levels were predictive for tumor response. Tumor response to chemotherapy was inversely correlated with the level of expression of RRM1 ($P = 0.001$; regulatory subunit of ribonucleotide reductase) and thymidylate synthase ($P = 0.006$). The authors concluded that the reduction in tumor size was greater in patients with low levels of gene expression. Smit et al conducted randomized phase II trial comparing pemetrexed with pemetrexed plus carboplatin in patients with relapsed NSCLC after platinum-based chemotherapy.⁴⁴ They analyzed polymorphisms of thymidylate synthase, the reduced folate carrier, γ -glutamyl hydrolase, and methylene tetrahydrofolate reductase (MTHF) to elucidate their potential roles as predictive biomarkers. Patients with homozygous mutations for MTHFR C677T had a significantly increased progression-free survival compared with patients with wild-type or heterozygous mutations ($P = 0.03$). Patients with homozygous mutations for MTHFR 1298C had a lower progression-free survival compared with those who had wild-type or heterozygous mutations, but did not quite reach statistical significance ($P = 0.06$). Progression-free survival did not differ for the other genotypes tested. The authors did not find any correlation between high and low thymidylate synthase expression genotype and tumor histology or clinical outcome. A more relevant clinical predictor of response to pemetrexed may be to analyze thymidylate synthase expression in the tumor itself. Further studies are needed to assess this possibility. Other investigators have also studied pemetrexed and its potential synergy with other agents to try and predict tumoral response at the molecular level. Giovannetti et al examined pemetrexed and its synergy *in vitro* with erlotinib⁴⁵ and

gemcitabine⁴⁶ in separate studies against NSCLC tumor cells. Both experiments showed synergistic cytotoxicity and enhanced apoptosis. These results, combined with predictive biomarkers for pemetrexed efficacy, provide a powerful foundation for future research to better tailor therapy for patients with advanced NSCLC.

Pemetrexed has clearly been proven an effective and well-tolerated therapy in the treatment of advanced NSCLC in both first- and second-line settings. Its role in maintenance therapy is still being defined, as is the concept of maintenance therapy as a whole. However, without a clearly defined advantage over administering second-line therapy at the time of disease progression, maintenance regimens are an expense that may not be justified in this emerging era of cost-conscious health care. With so many trials failing to show any significant overall survival benefits, one wonders how many times this well can be tapped. Meanwhile, the goal of personalizing therapy appears to hold the key to improving outcomes for patients in future treatment paradigms.

Disclosures

The authors declare no conflicts of interest.

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