Clinical Medicine Reviews in Oncology

REVIEW

Maintenance Therapy of Patients with Advanced or Metastatic Non-Squamous Non-Small Cell Lung Cancer—Role of Pemetrexed

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Abstract: Although progress could have been achieved in treatment of patients with advanced non-small cell lung cancer (NSCLC), outcome still remains poor. One of the strategies to improve survival currently under investigation is maintenance therapy, e.g. prolongation of treatment duration with the administration of an agent at the end of a defined number of initial chemotherapy cycles. This can consist of molecularly targeted or chemotherapeutic drugs which were already included in the induction therapy or different, potentially noncross-resistant agents. The latter represents the perhaps most promising strategy according to currently available data. Drugs chosen for this form of maintenance should be well tolerated with favorable toxicity profile. In the search for this, pemetrexed has classified as an encouraging agent for maintenance therapy as it can be easily delivered, has a favorable toxicity profile and has already demonstrated significant efficacy in advanced NSCLC. Here we review the current status of maintenance therapy with emphasis on pemetrexed in advanced NSCLC.

Keywords: pemetrexed, maintenance therapy, lung cancer

Clinical Medicine Reviews in Oncology 2010:2 263–271

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Introduction

Lung cancer remains a major cause of cancer mortality, accounting for more than a million deaths per year worldwide.[1] About 80% of these tumors are non-small cell lung cancers (NSCLC). NSCLC is often diagnosed at an advanced stage, comprising metastatic (stage IV) and recurrent disease, or locally advanced stages (stage III) which are not amenable to curative therapeutical options. Evidence about the benefit of platinum-based doublets over best supportive care as first-line treatment of advanced NSCLC has been demonstrated earlier by a landmark meta-analysis.[2] However, prognosis of patients with advanced NSCLC remains poor. Recent randomized phase III trials have shown that platinum-based chemotherapy combination regimens yield a median survival of 8–11 month with a 1-year survival rate of 30%–45% and a 2-year survival rate of 10%–20%.[3–6] Yet, the efficacy of standard platinum-based doublets has reached a plateau in first-line therapy for these stages. Consequently, several new therapeutical approaches have been evaluated in an attempt to improve patient outcome. In this context, novel molecular targeted agents such as bevacizumab and cetuximab in combination with chemotherapy are associated with modest improvement in overall survival.[7,8] Other treatment approaches included the evaluation of three-drug chemotherapy combinations in comparison to standard doublets with disappointing results: while efficacy was not improved, the toxicity profile was worse.[9] Furthermore, continuation of combination chemotherapy beyond four to six cycles only results in added toxicity without a meaningful improvement in overall survival.[10] Yet, a recent meta-analysis showed that extending chemotherapy beyond a standard number of cycles was associated with a clinically substantial and significant improvement in progression-free survival however with higher rates of adverse events and possible impairments of health related quality of life.[11] Therefore a "wait and watch" approach is frequently chosen after achieving maximal response to initial therapy. Still, in patients this "drug holiday" is often associated with anxiety about disease recurrence or progression coupled with concern for clinical deterioration and the inability to receive subsequent therapy. Additionally, the relatively brief duration of disease control even after a marked response to 1st line therapy resulted in the evaluation of further strategies to delay progression and improve overall survival in advanced NSCLC. One of the strategies currently under investigation is maintenance therapy after first-line chemotherapy.

Role of Maintenance Therapy in NSCLC

Maintenance therapy is defined as the prolongation of treatment duration with the administration of an agent at the end of a defined number of initial chemotherapy cycles, after achieving a complete or partial response (CR/PR) or disease stabilization (SD) in an individual patient. It is aimed to be administered until evidence of disease progression in the absence of significant toxicity. When therapy is continued for a defined time, the term "consolidation treatment" is often chosen. Maintenance therapy comprises either a chemotherapeutic drug or a molecularly targeted agent and includes drugs already used in the induction regimen or consists of a different, potentially non-crossresistant agent. The availability of well-tolerated new drugs which are suitable for prolonged administration without serious cumulative toxicity led to a renewed interest in maintenance therapy in NSCLC.

Prior studies in lung cancer failed to demonstrate a substantial benefit in terms of prolonged overall survival.[12–15] However, most of the regimens tested were associated with a too marked toxicity for maintenance or prolonged therapy which led to a high degree of patient withdrawal in these studies. Moreover, most regimens tested would nowadays be classified as minor effective in comparison to currently available novel agents. Studies on maintenance therapy with chemotherapy agents already present in the induction phase showed improved progression free survival for paclitaxel and for gemcitabine compared to best supportive care only.[16,50] Regarding molecularly targeted drugs several studies explored the role of maintenance therapy with agents who were already present in the induction phase such as bevacizumab, cetuximab, gefitinib and erlotinib with variable results.[7,8,17–22]

More recent studies investigated the role of newer drugs as maintenance therapy which were not included in the induction phase. Administering a different therapeutic regimen after induction therapy might have some theoretical advantages: the early

use of a potentially non-crossresistant therapy might circumvent or at least delay the development of chemotherapy-resistance. Moreover, patients with a response or tumor stabilization could benefit from a maintenance therapy when tumor burden is low. In addition, newer, third-generation or targeted drugs might be more effective with a good tolerability, and therefore it should be possible to extend therapy for a longer treatment-duration. In regard to this, several studies were able to demonstrate a statistically significant improvement of progression free survival (PFS).[23–27] Additionally, in two studies, a significant improvement of overall survival (OS) was noted.[23,24] One study by Fidias et al analyzed the effect of maintenance treatment with docetaxel versus docetaxel as second-line treatment after disease progression after four cycles of first-line therapy with carboplatin and gemcitabine. Besides a statistical significant prolongation of PFS, an advantage of overall free survival of about 3 months was noted, yet this failed to reach statistical significance. Substantial criticism noted that a benefit for maintenance in this study might only be attributed to a higher proportion of patients receiving active therapy in this treatment arm.[26] Other trials analyzed the effect of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors: Hida and coworkers[27] investigated the role of gefitinib after platinum-based therapy demonstrating a significant longer overall survival for adenocarcinoma and a longer progression free survival for all patients in the gefinitib arm. In the SATURN study[24] erlotinib, an inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase, was compared to placebo after 4 cycles of a platinum-doubled. Therapy with erlotinib resulted in a statistically significant improvement in PFS (HR 0.71; median 12·3 versus 11·1 weeks) and overall survival (HR 0.81; median 12·0 versus 11·0 months). Quality-of-life indices did not show significant differences between the treatment groups while the toxicity profile was consistent with that of previous studies on erlotinib. Moreover, treatment with the EGFR tyrosine kinase inhibitor was associated with a favourable HR of 0.10 ($P < 0{\cdot}0001$) for patients with an EGFR mutation. However, this difference did not translate into a significant improvement in overall survival. The ATLAS study[25] sought to determine whether the combination of bevacizumab and erlotinib is more effective than bevacizumab alone as maintenance therapy after a frontline therapy with a platinum-based chemotherapy. Preliminary data were able to demonstrate a modest improvement in the primary endpoint progression free survival with the combination maintenance therapy. Moreover, these data showed a trend towards a weak prolongation of overall survival (15.9 vs. 13.9 months), but the study was not powered to detect OS difference.[25] Besides, this study was not aimed to address the potentially more relevant question of the role of maintenance therapy with bevacizumab alone.

Clinical Studies on Pemetrexed as Maintenance Therapy in NSCLC

In the search for well tolerated and efficient chemotherapeutic drugs, pemetrexed is also being evaluated in the maintenance setting.

Pemetrexed is a multitargeted antifolate, whose further pharmacological attributes will be described below. Several trials have already proven efficacy in patients with advanced NSCLC, and it was approved in 2004 by the U.S. Food and Drug Administration (FDA) as second-line therapy in patients with previously chemotherapy treated advanced NSCLC.[28] In 2008, Scagliotti[29] published results from a phase III study about pemetrexed in the first line therapy in advanced NSCLC. In this study, the combination of pemetrexed and cisplatin was shown not to be inferior in regards to overall survival compared to cisplatin and gemcitabine for all patients assessed. Moreover, the pemetrexed-cisplatin doublet significantly improved survival in patients with non-squamous NSCLC. The most probable reason for this finding is the differential expression of thymidylate synthase in squamous and non-squamous lung cancer. The results of this study led to the approval of pemetrexed in combination with cisplatin for patients with advanced or metastatic NSCLC other than predominantly squamous cell histology. As to toxicity for the cisplatin/pemetrexed combination both hematologic and non-hematologic toxicities were significantly favourable, which has also been described in other studies before.[28] As this doublet can be easily delivered with good tolerability and relatively low toxicity, it is also under evaluation for further indications in NSCLC, e.g. in the adjuvant setting after curative intent surgery.[30]

On the basis of its efficacy in NSCLC and its favourable toxicity profile, Pemetrexed was also assessed as maintenance therapy in patients with advanced NSCLC—either as maintenance therapy in which pemetrexed was already present in the induction phase[31,32] or which added pemetrexed after an induction therapy with chemotherapeutic drugs other than pemetrexed.[23]

In a phase II trial in chemotherapy-naive advanced (stage IIIB or IV) non-squamous NSCLC patients, patients were treated with 6 cycles of carboplatin, pemetrexed and bevacizumab.[32] For patients with stable disease or a partial response, pemetrexed (500 mg/m^2) and bevacizumab (15 mg/kg) were continued every 3 weeks until disease progression or significant toxicity. 50 patients were enrolled and received a median of 7 treatment cycles. Among 49 patients assessable for response, the objective response rate was 55% (95% confidence interval [CI], 41%–69%) with a median PFS of 7.8 months (95% CI, 5.2–11.5 months) and a median OS of 14.1 months (95% CI, 10.8–19.6 months). Grade 3/4 toxicity was moderate with neutropenia in 4%, anemia 6%, thrombocytopenia 8%, fatigue 8%, infection 10% and thromboembolic events in 8%. The authors concluded that the combination of a platinum based induction therapy and maintenance therapy with both pemetrexed and bevacizumab in patients with non-squamous NSCLC is feasible with an acceptable toxicity profile with encouraging activity.

As carboplatin is widely used as a substitute for cisplatin in clinical practice, Okamoto et al[31] investigated in a phase I dose-escalation study the optimal dose of pemetrexed and carboplatin in patients with chemo-naive advanced NSCLC. Patients received escalated doses of carboplatin area under the concentration–time curve (AUC) of 5 (cohort 1) or 6 (cohort 2) and pemetrexed 500 mg/m^2 every 3 weeks for six cycles. For patients with objective response or stable disease, pemetrexed was continued until disease progression or unacceptable toxicity. A dose-limiting toxicity was only observed in one of six patients in cohort 1 and no dose limiting toxicities were seen in the first 6 patients of cohort 2. Therefore, the combination pemetrexed 500 mg/m^2 and carboplatin AUC 6 was defined as the recommended dose within the study. A total of 20 patients were treated and 8 patients received a median of 4 cycles of pemetrexed maintenance therapy without unexpected or cumulative toxicities. However, hematological adverse events reaching ≥grade 3 reported were neutropenia (75%), anemia (50%), thrombocytopenia (45%) and leukopenia (15%). 12 partial responses and no complete responses were observed, resulting in an overall response rate of 60.0% [95% CI, 36.1%–80.9%]. Median progression-free survival time for all patients was 7.6 months (95% CI: 4.8–8.0 months). Therefore the authors concluded that pemetrexed 500 mg/m^2 plus carboplatin AUC 6 combination therapy followed by pemetrexed maintenance therapy, is generally tolerable, and shows encouraging antitumor activity in chemotherapy-naive patients with advanced NSCLC.[31]

In a double blind phase III trial by Ciuleanu et al[23] the efficacy and safety for pemetrexed compared to placebo was assessed in stage IIIB/IV NSCLC patients who had not progressed after 4 cycles of a platinum-based induction chemotherapy. This induction therapy consisted of gemicitabine or docetaxel or paclitaxel with cisplatin or carboplatin. The 2:1 randomization was balanced for stage, ECOG performance status score, sex, response to induction therapy, combination partner to platin and brain metastases. Patients received either pemetrexed (500 mg/m^2, day 1) or i.v. placebo both plus vitamin B12 and folic acid supplementation and plus best supportive care every 3 weeks until disease progression. Primary endpoint was progression-free, secondary endpoint overall survival. 663 patients were enrolled into the study of which 441 were assigned to the pemetrexed arm and 222 to placebo. Pemetrexed significantly improved PFS with 4.3 month (95% CI 4.1–4.7) versus 2.6 month in the placebo arm (95% CI 1.7–2.8) with a hazard ratio (HR) of 0.50, $P < 0.0001$; moreover, overall survival was significantly prolonged by pemetrexed (13.4 month (95% CI 11.9–15.9) versus 10.6 month (95% CI 8.7–12.0), HR 0,79, $P = 0.012$). Furthermore, treatment with pemetrexed was relatively well tolerated, with no drug-related deaths. Treatment discontinuations due to drug-related toxic effects occurred in 5% in the pemetrexed versus 1% in the placebo group. Drug related grade 3 or 4 toxic effects were higher with 16% for pemetrexed versus 4% in the placebo arm ($P < 0.0001$). Neutropenia after pemetrexed therapy only occurred in 3% versus 0% ($P = 0.006$) with febrile neutropenia in <1% of the cases (Table 1). Compliance with maintenance

Table 1. Drug-related toxic effects in maintenance pemetrexed versus placebo after platin-based induction chemotherapy (n.a. = not available) (according to [23]).

	Pemetrexed n = 441	Placebo n = 222	*P*-value
Therapy related death	0%	0%	1.000
≥1 grade 3/4 side effects	16%	4%	<0,0001
Therapy-related CTC Grade 3/4 toxicity			
Anemia	3%	<1%	n.a.
Neutropenia	3%	0%	0,006
Fatigue	5%	<1%	0,001

therapy was high with 87% for pemetrexed and 81.3% for placebo. In this trial, a prespecified analysis with regards to histology was performed, which also demonstrated a treatment-by-histology interaction for pemetrexed with better efficacy in non-squamous NSCLC (PFS HR 0.44; OS HR 0.7). Yet, in patients with squamous NSCLC PFS, OS and disease control rate did not differ significantly in the pemetrexed versus the placebo treatment (Table 2). The results of this study led to the approval of pemetrexed for the maintenance treatment of patients with advanced non-squamous NSCLC who have not progressed after platinum treatment by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) in 2009. One limitation of the study is that it did not include pemetrexed induction regimens, especially with regards to histology. Therefore, a current phase 3 double blind placebo-controlled study has been initiated to assess the safety and efficacy of maintenance pemetrexed after induction treatment with a cisplatin-pemetrexed doublet in patients with advanced non-squamous NSCLC with an estimated study completion date of mid 2011 (registered under ClinicalTrials.gov, NCT00789373). Another limitation of this study is that 51% of the patients in the pemetrexed arm (and 67% in the placebo arm) received systemic post-discontinuation anticancer therapies with only 18% crossover from the placebo to the pemetrexed group. This led to the debate that maintenance therapy with pemetrexed might not be superior to using pemetrexed as second-line therapy as soon as there is evidence of relapse or disease progression.[33] Also, criticism concerned the studies design on comparing an active compound versus placebo instead of the probable more relevant question to analyze the effect of maintenance treatment with pemetrexed versus pemetrexed as second-line treatment after disease progression after first line therapy. Furthermore, criticism appeared because patients did not receive bevacizumab as part of their first-line therapy and therefore the benefit of pemetrexed maintenance therapy might not be translated to patients with bevacizumab containing induction regimens.[33] Yet, in the phase 2 trial by Patel et al the combination of a platinum based induction therapy and maintenance therapy with both pemetrexed and bevacizumab in patients with non-squamous NSCLC was shown to be feasible with an acceptable toxicity profile with

Table 2. Efficacy by histology in maintenance pemetrexed versus placebo after platin-based induction chemotherapy (according to [23]).

Histology	Median progression free survival (months)			Median overall survival (months)		
	Pemetrexed	Placebo	*P*-value (hazard ratio)	Pemetrexed	Placebo	*P*-value (hazard ratio)
Non-squamous NSCLC (n = 481)	4,5	2,6	<0,0001 (0,44)	15,5	10,3	0,002 (0,70)
Adenocarcinoma (n = 328)	4,7	2,6	<0,0001 (0,45)	16,8	11,5	0,026 (0,73)
Large cell carcinoma (n = 20)	3,5	2,1	0,109 (0,40)	8,4	7,9	0,964 (0,98)
Other (n = 133)	4,2	2,8	0,0002 (0,43)	11,3	7,7	0,025 (0,61)
Squamous cell carcinoma (n = 182)	2,8	2,6	0,039 (0,69)	9,9	10,8	0,678 (1,07)

encouraging activity.[32] Moreover, an ongoing trial (ClinicalTrials.gov ID NCT00961415) tries to clarify this issue.

Mechanism of Action, Metabolism and Pharmacokinetic Profile of Pemetrexed

Natural folates are vital in humans for the production and maintenance of new cells, for DNA synthesis and RNA synthesis. For example, they serve as carriers of one-carbon moieties which are essential for synthesis of thymidine monophosphate (dTMP), an essential precursor for DNA synthesis, that is catalyzed by thymidylate synthase (TS). Moreover, folates are involved in remethylation of homocysteine, DNA methylation, regulation of chromatin structure, as well as methylation of proteins and drugs. Due to the essential role of DNA synthesis in rapidly dividing cancer cells, anti-metabolites such as the antifolate methotrexate and fluorouracil, a noncompetitive inhibitior of thymidylate synthase, have been used to treat various malignancies.[34,35]

Pemetrexed disodium is a multitargeted compound that acts by interfering with the binding of natural folate cofactors to important biosynthetic enzymes, thus inhibiting the growth of cancer cells.[35] Besides its primary target thymidylate synthase (TS), it also inhibits further folate dependent enzymes involved in the *de novo* biosynthesis of thymidine and purine nucleotides such as dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyl transferase (GARFT) (Fig. 1).

Upon uptake of the drug, pemetrexed is transported intracellularly predominantly through the reduced folate carrier system and metabolized to polyglutamated forms which is believed to play important roles in determining both the selectivity and the antitumor activity of this agent. While pemetrexed monoglutamate is only a weak inhibitor of GARFT and a modest inhibitor of TS, the polyglutamated forms have a much greater affinity for these enzymes.[36] Interestingly, the inhibitory activity of pemetrexed against DHFR, another target of pemetrexed, is not increased by polyglutamation. As an unchanged parent compound, pemetrexed undergoes predominantly rapid renal elimination

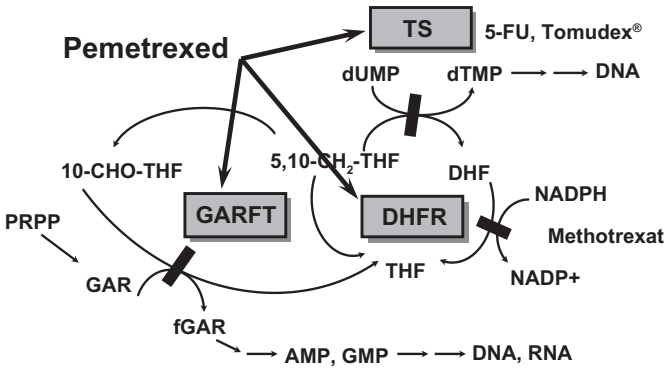

Figure 1. Inhibition of multiple folate-requiring enzymes by pemetrexed and its polyglutamated metabolites.
Abbreviations: TS, thymidylate synthase; DHFR, dihydrofolate reductase; GARFT, glycinamide ribonucleotide formyl transferase; THF, Tetrahydrofolate; DHF, Dihydrofolate [according to 49].

with a terminal half-life of between two to five hours. While vitamin B12, folic acid and low doses of aspirin do not seem to affect the pharmacokinetics of pemetrexed, higher doses of aspirin or other non-steroidal anti-inflammatory drugs such as ibuprofen (400 mg taken four times daily) may reduce pemetrexed clearance.

The endogeneous levels of thymidine and hypoxanthine play important roles for the inhibition of TS and GARFT, respectively. However, the growth-inhibitory effect of pemetrexed could not be prevented by hypoxanthine, but it was decreased by thymidine, and completely prevented by a combination of thymidine and hypoxanthine.[37,38]

Moreover, it was observed in both clinical and preclinical studies that elevated baseline total plasma homocysteine and methylmalonic acid levels were correlated with higher risk for severe toxicity.[36,39] Since conditions of folate and/or cobalamin deficiency increase total plasma homocysteine concentrations and cobalmain deficiency will lead to an increase in methylmalonic acid, the supplementation of both vitamins has been introduced into the therapeutic setting.

Pemetrexed for injection is supplied as a single-use sterile lyophilized powder for i.v. infusion in glass vials. Each 500 mg vial of pemetrexed contains 713 mg pemetrexed disodium heptahydrate equivalent to 500 mg pemetrexed free acid.[40] At least one week prior to application of the first dose of pemetrexed, folic acid and vitamin B12 supplementation should be initiated.

The pharmacokinetic disposition of pemetrexed does not appear to be affected in the presence of third space fluid such as pleural effusions.[41] However, till date, it is recommended that third space fluids be controlled before pemetrexed administration.[40]

Patient Preference and Place in Therapy for Maintenance Therapy

Following first line therapy, many patients remain asymptomatic and have good performance status. However, at the time of relapse or progression, patients often experience significantly more symptoms (e.g. anorexia, fatigue, dyspnea, and cough) and declining performance status. Despite the fact, that second line therapy has demonstrated improved survival and significant symptom palliation, only 50% to 60% of advanced NSCLC patients can receive second line therapy, and these patients generally represent a selected subgroup with a better overall prognosis.[42,44] Poor performance status is a major reason that patients cannot receive second line therapy and worsening of disease-related symptoms is associated with disease progression and death. Moreover, performance status and disease-related symptoms often worsen between first and second line chemotherapy, such that the practice of delaying second line therapy until disease progression may result in less tolerance to additional lines of therapy. Therefore, maintenance therapy with a non-cross resistant drug instead of adopting the wait and watch approach and continuing treatment at disease progression could allow patients to receive early one more potentially active drug with an acceptable increase in toxicity. In conclusion, maintenance therapy should be discussed with patients who had not progressed after platinum-based induction chemotherapy.[7,8,29,42–45] Especially patients with a high tumor volume and persistent symptomatic disease should be strongly considered for maintenance therapy. However, the benefit of this therapy has to be balanced with the potential increase in toxicity. Moreover, it has to be critically discussed with the patients that a significant, but relatively moderate benefit in survival might be at the expense of an impaired quality of life as shown in the meta-analysis by Soon et al.[11] Therefore, recent guidelines advise clinicians to assess the patient's preferences and the accuracy of his or her perception of the risks and benefits involved in therapy for advanced stage NSCLC. Besides the potential outcome improvement and the additional burden to patients, the resource use and cost involved with this therapy have to be weighted on an individual patient basis. Current guidelines still lack a clear statement towards maintenance therapy (ASCO guideline 2009).[46]

Outlook—Predictive Markers

Intensive research has been undertaken to identify subgroups of patients that are most likely to benefit from a respective treatment. Besides histological subgroups as demonstrated by phase III trials,[29] tumor cell expression of TS may be a potential biomarker with respect to response to pemetrexed. Preclinical data have suggested that overexpression of TS correlates with reduced sensitivity to pemetrexed and antifolate resistant cell-lines.[47] Moreover, Thymidylate synthase, the main target of pemetrexed, was found to be differentially expressed among the histotypes of lung cancer, being lower in adenocarcinoma and higher in squamous cell and small-cell lung cancer.[48] However, prospective randomized trials are pending, and various questions regarding assessing TS expression in a standardized fashion remain to be addressed before any conclusions can be made.

Conclusions

Current guidelines recommend a limited number of first-line chemotherapy for advanced NSCLC. However, the early use of an anticancer agent as maintenance therapy after disease stabilization or maximal response with platinum-based regimens is being recognized as a new treatment paradigm in NSCLC. An optimal maintenance therapy should improve outcome, be well-tolerated and be devoid of cumulative toxicity. Treatment with pemetrexed, a multi-targeted antifolate, in the maintenance setting results in significant improved survival for patients with advanced non-squamous NSCLC. Furthermore, it was shown to be well tolerated without treatment related-deaths and only few severe adverse events. Consequently, pemetrexed has been approved in this setting for patients with advanced

non-squamous NSCLC. Taken together, the current data provide evidence to support the administration of maintenance therapy in selected patients with advanced stage non-squamous NSCLC with pemetrexed. Besides this compound, maintenance therapy with the EGFR tyrosine kinase inhibitor erlotinib might represent a notable alternative. However, the decision to administer maintenance therapy should respect patient preferences and consider disease burden, symptoms and the potential toxicities as well as toxicities associated with first-line therapy. Furthermore, in future clinical trials quality of life should be more emphasized and there is a strong need to establish the best agent for different patient populations.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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