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Pemetrexed Monotherapy for the Maintenance Treatment
of Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer
with Non-Squamous Histology

S. Cheng, A.E. Haynes, A. Robinson, and Y.C. Ung

Report Date: March 3, 2011

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SUMMARY

QUESTION

Does the use of pemetrexed monotherapy for the maintenance treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with non-squamous histology result in improved outcomes?

The outcomes of interest are overall survival (OS), progression-free survival (PFS), time-to-progression (TTP), time-to-next-treatment, complete response (CR), objective response (OR), duration of response, time to response, quality of life (QOL), and adverse effects.

TARGET POPULATION

Adult patients with locally advanced (stage IIIB) or metastatic (stage IV) NSCLC with non-squamous histology who have recently completed first-line platinum-based doublet induction chemotherapy.

RECOMMENDATIONS

The following recommendations reflect the opinions of the authors of this special advice report.

- Pemetrexed switch maintenance is a reasonable treatment option after platinum-based doublet induction chemotherapy for a select population of patients with non-squamous stage IIIB or IV non-small cell lung cancer. Further research is required to identify patients that may derive benefit from switch maintenance pemetrexed versus those who may safely have a treatment interruption before beginning second-line pemetrexed chemotherapy.

QUALIFYING STATEMENTS

- The authors of this report use the term “switch maintenance” when the chemotherapeutic agent used for maintenance therapy is not one of the chemotherapeutic agents that was used during induction chemotherapy.
used during induction therapy.

- Pemetrexed switch maintenance is a reasonable treatment option for a select population of patients with stage IIIB or IV NSCLC after platinum-based doublet induction chemotherapy. In the opinion of the authors, such patients may include those with good performance status (ECOG 0-1) post-induction chemotherapy and with complete or partial response or stable disease to induction chemotherapy. There may be a select population of patients with epidermal growth factor receptor (EGFR) activating mutations that may not derive benefit from this approach. These patients would represent the select population for which further research is needed. There may also be a select population of patients with indolent disease or durable remission post first-line platinum-based doublet that may not benefit from switch maintenance pemetrexed. Clinical discretion should be used in these incidences until such evidence exists.

- Pemetrexed switch maintenance should be administered at 500 mg/m² intravenously on day 1 of a 21-day cycle until disease progression. Treatment should begin no earlier than 21 days and no later than 42 days after the first day of the patient’s last cycle of induction therapy. Although the median number of cycles of maintenance pemetrexed was five in the study, it is the opinion of the authors that a restriction on the number of cycles of therapy should not exist pending continual response or stable disease or toxicity.

KEY EVIDENCE

One randomized controlled trial (1) was identified that investigated the use of switch maintenance with pemetrexed in patients with non-squamous histology stage IIIB or IV non-small cell lung cancer. The authors randomized 663 patients in a 2:1 ratio to receive switch maintenance with pemetrexed or to receive placebo. All patients received best supportive care. The authors reported that for 481 patients with non-squamous histologies, a significant difference in favour of pemetrexed switch maintenance compared to placebo was found for both the primary outcome, progression-free survival (median, 4.5 months versus [vs.] 2.6 months, respectively; HR 0.44, p<0.0001), and for overall survival (median, 15.5 months vs. 10.3 months; HR 0.70, p=0.002). As the endpoint for progression-free survival was progression or death, and given that neither arm received second-line therapy until progression, the authors of this report agree that the observed benefit in progression-free survival was likely due to the use of pemetrexed as switch maintenance therapy.

Despite the beneficial effects of pemetrexed switch maintenance therapy in terms of progression-free survival, there are methodological issues with the identified RCT that complicate the interpretation of the results with respect to overall survival. Specifically, it is important to note that a majority of patients randomized to the placebo arm never received an effective second-line therapy. Only 29% of patients in the placebo arm received docetaxel as second-line or later treatment. In addition, only 18% of patients in the placebo arm received pemetrexed as second-line or later treatment. In an Evidence-based Series published in 2006, the Lung Cancer Disease Site Group recommended either docetaxel or pemetrexed for the second-line treatment of advanced or metastatic non-small cell lung cancer (2). As Ciuleanu et al (1) did not report how many patients may have received more than one additional line of therapy, it is impossible to know exactly how many patients received either docetaxel or pemetrexed as second-line therapy. Hence, the actual percentage of patients who received either agent as an appropriate second-line therapy is unclear. It is also unknown whether patients in the placebo arm were allowed to continue docetaxel or pemetrexed until disease progression or if patients received only a finite number of cycles.

The results of the trial suggest that pemetrexed is beneficial in prolonging disease control and improving survival in patients with non-squamous histology locally advanced or
metastatic non-small cell lung cancer (1). The benefits in overall survival shown in the trial may be due to a number of different factors, including the following:

- A minimum of 51% of patients in the switch maintenance arm received a platinum doublet combination followed by pemetrexed, then followed by at least one additional line of systemic chemotherapy. Hence, it may be concluded that more patients in the study arm received two or more lines of therapy compared to the placebo arm.
- The early introduction of a second-line agent in the switch maintenance pemetrexed arm could have lead to the increased anti-tumour activity of pemetrexed.
- All patients on the switch maintenance arm received pemetrexed, whereas only 18% of patients on the placebo arm received pemetrexed.
- Most importantly, at least twice as many patients in the switch maintenance pemetrexed arm had access to an effective second-line agent at some point in their treatment course than patients in the placebo arm (100% of patients in the switch maintenance arm received a platinum doublet then pemetrexed switch maintenance, compared to 47% of patients in the placebo arm who received an effective second-line therapy: either pemetrexed [18%] or docetaxel [29%]).

Generally, less than 50% of patients proceed to second line chemotherapy for Stage IIB/IV non-small cell lung cancer (3). The benefit in progression free survival and overall survival seen in this study may be due to the early introduction, 100% enrolment and good tolerability of an effective agent (pemetrexed) post induction chemotherapy.

It should be noted that 43% and 57% of patients in the switch maintenance arm received platinum based therapy with taxanes and non-taxanes, respectively in the induction phase. As second/third-line therapy in the switch maintenance arm, 22% received docetaxel, 35% received an EGFR inhibitor, 9% gemcitabine, and 13% vinorelbine. In the absence of definitive data, it is reasonable to conclude that use of any of these agents in the second-line setting would be acceptable options after switch maintenance therapy with pemetrexed.

FUTURE RESEARCH
Future research should investigate a treatment strategy including closer follow-up from first-line and earlier introduction of second-line therapy in comparison to a treatment strategy using switch maintenance. In addition, the continued use of second-line therapies until diseases progression, and therefore beyond the current funding limit of six cycles, needs to be investigated.

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Evidence-based Series
• #7-10 v2.2010: First Line Systemic Chemotherapy in the Treatment of Advanced Non-Small Cell Lung Cancer.
  Available at: http://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/lung-ebs/.

• #7-19: Second Line or Subsequent Systemic Therapy for Recurrent or Progressive Non-Small Cell Lung Cancer.
  Available at: http://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/lung-ebs/.
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REFERENCES—SUMMARY


QUESTION

Does the use of pemetrexed monotherapy for the maintenance treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with non-squamous histology result in improved outcomes?

The outcomes of interest are overall survival (OS), progression-free survival (PFS), time-to-progression (TTP), time-to-next-treatment, complete response (CR), objective response (OR), duration of response, time to response, quality of life (QOL), and adverse effects.

INTRODUCTION

The estimated incidence of lung cancer in Canada in 2010 is 55 new cases per 100,000 people (1). Approximately 85% of those cases will be NSCLC, and of those, 45-55% will present with stage IIIB or IV NSCLC.

The Lung Cancer Disease Site Group (Lung DSG) of Cancer Care Ontario’s (CCO) Program in Evidence-based Care (PEBC) published a guideline on first-line systemic chemotherapy in patients with advanced NSCLC in February 2010 (2,3). The Lung DSG recommended platinum-based doublet chemotherapy (i.e., platinum in combination with a new agent) as first-line therapy in advanced NSCLC as it can provide a modest increase in survival (2,3). The Lung DSG also recommended continuing chemotherapy beyond three to four cycles but stopping after four to six cycles of therapy. The DSG felt that although no survival benefit had been demonstrated, the majority of trials were not powered to detect small differences in survival and that chemotherapy given for longer than three to four cycles is likely to improve PFS, but may lead to worsened toxicity and perhaps quality of life.

Maintenance chemotherapy refers to the continuation of the same chemotherapy agents as those used in induction therapy, until radiographic disease progression (4). Maintenance therapy is offered to patients who have achieved a complete or partial response, or stable disease, after induction chemotherapy. Consolidation therapy generally refers to the use of a different agent (following induction) prior to radiographic disease progression for a finite number of cycles (4,5). The rationale for offering maintenance treatment is that prolonging therapy could continue to eradicate “sensitive clones” that persist following induction chemotherapy, which could slow disease progression and improve symptom control in patients who prove to be chemosensitive.

Understandably, therefore, the definitions of “maintenance” and “consolidation” chemotherapy have not been completely clear. The terms have been used interchangeably at times; however, the theoretical targets are different. Consolidation is meant to destroy different clones of cancer cells, while maintenance is meant to continue the destruction of sensitive clones. The authors of this report use the term “switch maintenance” when the chemotherapeutic agent used for maintenance therapy is not one of the chemotherapeutic agents that was used during induction therapy.

Pemetrexed is an antifolate that affects antineoplastic action by disrupting folate-dependent metabolic processes required for cellular replication (6). In a 2006 clinical practice guideline, the Lung DSG concluded that pemetrexed, as a single agent, is a recommended treatment option for the second-line therapy of recurrent or progressive advanced or metastatic NSCLC (7).

The objective of this special advice report (SAR) is to provide advice on the use of pemetrexed as a single-agent switch maintenance therapy in patients with advanced (stage IIIB or IV) NSCLC with non-squamous histology. This advice was requested by the Cancer Care Ontario-Committee to Evaluate Drugs (CCO-CED) Subcommittee and the Ontario Ministry of Health.
METHODS

This advice report, produced by the Program in Evidence-based Care (PEBC) of CCO, is a convenient and up-to-date source of the best available evidence on pemetrexed monotherapy as a maintenance treatment in patients with locally advanced or metastatic NSCLC with non-squamous histology, developed through a systematic review of the available evidence. Contributing authors disclosed any potential conflicts of interest. The PEBC is editorially independent of the Ontario Ministry of Health and Long-Term Care.

The PEBC has a formal standardized process to ensure the currency of each clinical guidance report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original clinical guidance report information.

Literature Search Strategy

MEDLINE (Ovid) (1950 to September Week 3, 2010 [October 1]), Medline Daily Update (OVID) (October 1, 2010), Medline In Process & Other Non-indexed Citations (OVID) (October 1, 2010), Embase (Ovid) (1980 to Week 39, 2010 [October 1]), and the Cochrane Library (October 1, 2010) databases were searched. The search strategies for MEDLINE and Embase are shown in Appendix 1. Search strategies in other databases were similar.

In addition, conference proceedings of the American Society of Clinical Oncology (ASCO), 2005 to 2010, were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnw/cpgs/index.asp), the National Guidelines Clearinghouse (http://www.guideline.gov/index.asp), and the National Institute for Clinical Excellence (http://www.nice.org.uk/) were also searched for existing evidence-based practice guidelines.

Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from these sources were searched for additional trials. Personal files were also searched.

Study Selection Criteria

Inclusion Criteria

1. Randomized trials comparing pemetrexed monotherapy as a maintenance treatment to placebo.
2. Trials including patients with locally advanced (stage IIIIB) or metastatic (stage IV) NSCLC with non-squamous histology.
3. Systematic reviews, meta-analyses, or practice guidelines investigating or providing advice on the use of pemetrexed monotherapy as a maintenance treatment in patients with locally advanced (stage IIIIB) or metastatic (stage IV) NSCLC with non-squamous histology.
4. Published studies reporting data on one or more of the following outcomes: OS, PFS, TTP, time-to-next treatment, CR, OR, time to response, duration of response, QOL, or adverse effects.

Exclusion Criteria

Studies were excluded if they were:
1. Practice guidelines that did not report whether a systematic literature search was conducted or the methods used to conduct the systematic literature search.
2. Letters, comments, books, notes, or editorial publication types.
3. Articles published in a language other than English, due to financial considerations for translation.
Synthesizing the Evidence

A meta-analysis of the trial results will be conducted if sufficient randomized trials of pemetrexed monotherapy as a maintenance treatment are identified, and a meta-analysis is appropriate.

RESULTS

Literature Search Results

A total of 495 citations were identified in the databases of MEDLINE, Embase, and the Cochrane Library (Figure 1). Two full publications describing two randomized controlled trials (RCTs) were identified (8,9). One publication (9) reported the protocol of an ongoing study but did not report results. Seventy abstracts were identified from the annual meeting proceedings of ASCO. Four abstracts of randomized trials were identified. Three of the abstracts (10-12) reported early results of the fully published RCT reported by Ciuleanu et al (8) and are therefore not referenced further. The remaining abstract (13) reported on the same ongoing RCT as Paz-Ares et al (9). That trial will not be discussed further as it is ongoing, and no results have yet been reported.

Figure 1. Selection of studies investigating pemetrexed monotherapy as maintenance treatment in patients with locally advanced or metastatic non-squamous NSCLC from the search results of MEDLINE, Embase, and the Cochrane Library databases, and the ASCO conference proceedings.

495 citations retrieved from Medline, Medline Daily Update, Medline In-Process & Other Non-Indexed Citations, EMBASE, and the Cochrane Library databases.

70 abstracts retrieved from the conference proceedings of ASCO.

66 excluded:
- not pemetrexed monotherapy;
- not a randomized trial;
- not maintenance therapy.

None excluded.

464 excluded:
- not pemetrexed maintenance
- not a randomized trial.
- not a systematic review, meta-analysis, or practice guideline.

31 citations retrieved for full publication review.

4 abstracts identified.

Title and abstract review by single author (AH).

Title and abstract reviewed by single author (AH).

Full publication review by two authors (AH, SC).

A total of 2 full publications and 4 abstracts detailing 2 unique RCTs were identified.

29 excluded:
- not pemetrexed monotherapy;
- not maintenance therapy.
- practice guideline that did not report a systematic literature search.
Patient Characteristics, Study Design, and Trial Quality

One RCT was identified that reported results for switch maintenance pemetrexed in patients with locally advanced or metastatic NSCLC. Ciuleanu et al (8) enrolled patients with a diagnosis of stage IIIB or IV NSCLC prior to induction therapy who had not progressed on four 21-day cycles of platinum-based chemotherapy (Table 1). Patients were randomized 2:1 to receive pemetrexed switch maintenance (n=441) or placebo (n=222) (Table 1). All patients received best supportive care. Of the 663 total patients, 481 had non-squamous histology with 325 of those randomized to pemetrexed switch maintenance and 156 randomized to placebo. Select quality characteristics of the RCT can be found in Table 2. The authors reported a sample size requirement (Table 2) and that for both the primary outcome of PFS and the secondary outcome of OS, that requirement was met. The study was double-blind and randomization was performed through a centralized, computer-based system that stratified patients for a number of factors, including disease stage (IIIB or IV), Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1), sex, best response to induction (complete or partial or stable disease), non-platinum component of induction therapy (gemcitabine or paclitaxel, or docetaxel), and history of brain metastases (yes or no). The authors reported the final, intention-to-treat analysis. The trial was not terminated early. In addition, the authors reported that the trial arms were balanced for a number of factors, including those by which patients were stratified as well as by histology (e.g., non-squamous, squamous).

Table 1. Trial and patient characteristics in trials investigating the use of pemetrexed maintenance in patients with locally advanced or metastatic non-squamous NSCLC.

<table>
<thead>
<tr>
<th>Author, year (ref)</th>
<th>Patient characteristics</th>
<th>Treatment</th>
<th>N</th>
<th>Number of pts with non-squamous histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciuleanu, 2009 (8)</td>
<td>Patients aged ≥18 years, life expectancy ≥12 weeks, ECOG PS 0 or 1, with diagnosis of stage IIIB or IV NSCLC prior to induction therapy and who had not progressed on four 21-day cycles of platinum-based chemotherapy. Eligible doublet regimens included any of the following in combination with either cisplatin or carboplatin: gemcitabine, paclitaxel, or docetaxel.</td>
<td>Pemetrexed 500 mg/m² i.v. d1 q21d, until disease progression. All patients received best supportive care.</td>
<td>441</td>
<td>325</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo i.v. d1 q21d, until disease progression. All patients received best supportive care.</td>
<td>222</td>
<td>156</td>
</tr>
</tbody>
</table>

Notes: d=day(s); ECOG=Eastern Cooperative Oncology Group; i.v.=intravenous; mos=months; N=number randomized; NSCLC=non-small-cell lung cancer; PS=performance status; pts=patients; q=every; ref=reference.
Table 2. Quality characteristics of identified RCT.

<table>
<thead>
<tr>
<th>Author, year (ref)</th>
<th>Primary outcome</th>
<th>Required sample size</th>
<th>Secondary outcomes</th>
<th>Randomization method</th>
<th>Allocation concealment</th>
<th>Blinding</th>
<th>ITT analysis</th>
<th>Final analysis</th>
<th>Early termination</th>
<th>Losses to follow-up</th>
<th>Ethical Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciuleanu, 2009 (8)</td>
<td>PFS</td>
<td>660 pts req’d to detect a PFS HR of 0.75 for Pem vs. placebo with a power of 85% and an OS HR of 0.767 for Pem vs. placebo with a power of 80%.</td>
<td>OS, OR^a, adverse effects</td>
<td>Computer-based and centralized with stratification</td>
<td>Yes</td>
<td>Double-blind^b</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>NR^c</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Notes: ITT=intent-to-treat; NR=not reported; OS=overall survival; PFS=progression-free survival; pts=patients; ref=reference; req’d=required; SRE=skeletal-related event; vs.=versus.
^aObjective response was defined by the authors as complete response plus partial response plus stable disease.
^bThe study was double-blinded, with the patients and the study team blinded to treatment assignment.
^cThe authors reported that 7.1% of patients discontinued treatment due to protocol violation, entry criteria not met, satisfactory response, loss to follow-up, or physician or sponsor decision. The authors did not specify how many of those were lost to follow-up. All patients were included in the final analysis.

Efficacy Outcomes

Efficacy outcomes for the identified RCT can be found in Table 3.

Table 3. Efficacy outcomes in trials of pemetrexed maintenance in patients with locally advanced or metastatic non-squamous NSCLC.

<table>
<thead>
<tr>
<th>Author, year (ref)</th>
<th>Treatment</th>
<th>N</th>
<th>CR+PR+SD (%)</th>
<th>Median PFS investigator (mos)</th>
<th>Median PFS independent^a (mos)</th>
<th>Median OS (mos)</th>
<th>Median follow-up (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciuleanu, 2009 (8)</td>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pem</td>
<td>441</td>
<td>52</td>
<td>4.3</td>
<td>4.0</td>
<td>13.4</td>
<td>11.2</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>222</td>
<td>33</td>
<td>2.6</td>
<td>95% CI 0.42-0.61; p&lt;0.0001</td>
<td>HR=0.50</td>
<td>2.0</td>
<td>10.6</td>
</tr>
<tr>
<td>Pem</td>
<td>325</td>
<td>58</td>
<td>4.5</td>
<td>4.4</td>
<td>15.5</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>156</td>
<td>33</td>
<td>2.6</td>
<td>95% CI 0.36-0.55; p=0.0001</td>
<td>HR=0.44</td>
<td>1.8</td>
<td>10.3</td>
</tr>
</tbody>
</table>

Notes: CI=confidence interval; CR=complete response; mos=months; N=number randomized; NR=not reported; OS=overall survival; Pem=pemetrexed; PFS=progression-free survival; PR=partial response; ref=reference; req’d=required; SD=stable disease.
^aAn independent review of patient outcomes was undertaken and included 387 patients in the pemetrexed group and 194 in the placebo group.

Survival

Ciuleanu et al (8) reported median OS was significantly higher for patients with non-squamous NSCLC who received pemetrexed switch maintenance compared to placebo (15.5 months versus [vs.] 10.3 month, respectively; HR, 0.70; p=0.002). For patients with any
histology locally advanced or metastatic NSCLC, OS was significantly higher for patients who received pemetrexed switch maintenance vs. placebo (Table 2). The median duration of follow-up was 11.2 months for patients in the pemetrexed switch maintenance arm and 10.1 months in the placebo arm.

**Disease Control**

Ciuleanu et al (8) reported two analyses of the primary outcome, PFS: one conducted as an intent-to-treat analysis by the study investigators, and the other conducted by an independent review panel of 387 patients, of any histology, from the pemetrexed switch maintenance arm and 194 patients, of any histology, from the placebo arm (Table 3). Both analyses demonstrated statistically significant higher median PFS for pemetrexed switch maintenance vs. placebo in patients with any histology (investigator: HR, 0.50; p<0.0001 and; independent: HR, 0.60; p<0.0001) and patients with non-squamous histology (investigator: HR, 0.44; p<0.0001 and; independent: HR, 0.47; p<0.0001).

The authors did not report data on duration of response, time-to-next treatment.

**Response**

Ciuleanu et al (8) reported objective response rates, defined as CR plus partial response (PR) plus stable disease, that were significantly higher in the pemetrexed arm compared to the placebo arm for patients with any histology (52% vs. 33%, p<0.0001) and for patients with non-squamous histology (58% vs. 33%, p<0.0001).

**Quality of Life**

QOL data were not extensively reported (8); however, the trial publication states that time to worsening of patient-reported symptoms was examined using the lung cancer symptom scale. The authors reported a significant delay in symptom worsening in favour of pemetrexed compared to placebo for pain (median 6.1 months vs. 4.6 months; HR, 0.76; 95% confidence interval [CI], 0.59 to 0.99; p=0.041) and for hemoptysis (medians not reported; HR, 0.58; 95% CI, 0.34 to 0.97; p=0.038). The authors reported that more detailed results would be published in a later publication, but that publication was not identified in our literature search.

**Adverse Events**

Grade 3 or 4 adverse events can be found in Table 4. The authors reported significant higher rates of grade 3 or 4 neutropenia (3% vs. 0%, p=0.006) and grade 3 or 4 fatigue (5% vs. <1%, p=0.001) in the pemetrexed switch maintenance arm compared to the placebo arm. Of note, three patients (0.7%) in the pemetrexed arm had febrile neutropenia. Overall, the rate of grade 3 or 4 adverse effects was higher in the pemetrexed arm compared to the placebo arm (16% vs. 4%, respectively; p<0.0001).
Table 4. Grade 3 or 4 adverse events in trials of pemetrexed maintenance in patients with locally advanced or metastatic non-squamous NSCLC.

<table>
<thead>
<tr>
<th>Author, year (ref)</th>
<th>Treatment</th>
<th>N</th>
<th>Nausea (%)</th>
<th>Vomiting (%)</th>
<th>Fatigue (%)</th>
<th>Neutropenia (%)</th>
<th>Anemia (%)</th>
<th>Leucopenia (%)</th>
<th>Anorexia (%)</th>
<th>Infection (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciuleanu, 2009 (8)</td>
<td>Pem</td>
<td>441</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>222</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>0</td>
<td>&lt;1</td>
<td>0</td>
<td>&lt;1</td>
<td>0</td>
</tr>
</tbody>
</table>

Notes: N=number randomized; Pem=pemetrexed; ref=reference.

DISCUSSION

The use of the term “maintenance” is potentially problematic with respect to the agent used and the timing of therapy. Depending on the publication, the terms “maintenance,” “consolidation,” or “early second-line therapy” could potentially have similar, if not the same, meaning. When the agent used during maintenance therapy is a continuation of an agent used during induction, there is consensus in the broader community that this should be referred to as maintenance. Where disagreement exists is when the agent used for maintenance was not used during induction therapy. Some believe that this should be termed maintenance, others as early second-line therapy or even consolidation. The authors of this report suggest that the term “switch maintenance” be used to describe this specific scenario in order to bring clarity to the use of the various terms.

Only one RCT of pemetrexed maintenance therapy in patients with advanced NSCLC has been completed and reported to date (8). That trial was of high quality and demonstrated that, in patients who had received induction chemotherapy with a platinum agent in combination with either gemcitabine, paclitaxel, or docetaxel, OS and PFS were both significantly higher for patients who received pemetrexed switch maintenance compared to placebo (Table 3). That difference was more pronounced in patients with non-squamous NSCLC (Table 3). As the endpoint for PFS was progression or death, and given that neither arm received second-line therapy until progression, the authors of this report agree that the observed benefit in PFS was likely due to the use of pemetrexed as switch maintenance therapy.

Despite the beneficial effects of pemetrexed switch maintenance therapy in terms of PFS, there are methodological issues with the identified RCT that complicate the interpretation of the results with respect to OS. Specifically, it is important to note that a majority of patients randomized to the placebo arm never received an effective second-line therapy. Only 29% of patients in the placebo arm received docetaxel as a second-line or later treatment. In addition, only 18% of patients in the placebo arm received pemetrexed as a second-line or later treatment. In an Evidence-based Series published in 2006, the Lung DSG recommended either docetaxel or pemetrexed for the second-line treatment of advanced or metastatic NSCLC (7). As Ciuleanu et al (8) did not report how many patients might have received more than one additional line of therapy, it is impossible to know exactly how many patients received either docetaxel or pemetrexed as a second-line therapy. Hence, the actual percentage of patients who received either agent as an appropriate second-line therapy is unclear. It is also unknown whether patients in the placebo arm were allowed to continue docetaxel or pemetrexed until disease progression or if patients received only a finite number of cycles. Conversely, 100% of the patients in the pemetrexed switch
maintenance arm received a platinum doublet then pemetrexed until disease progression. Therefore, at least twice as many patients in the switch maintenance arm had access to an effective second-line agent at some point in their treatment course compared to the placebo arm (100% of patients in the switch maintenance arm received a platinum doublet then pemetrexed switch maintenance compared to 47% of patients in the placebo arm who received an effective second-line therapy: either pemetrexed [18%] or docetaxel [29%]).

The uncertainty surrounding the benefit in OS is also partly due to the fact that all patients in the pemetrexed switch maintenance arm received pemetrexed at some point in their treatment and that, at most, only 18% of patients in the placebo arm received pemetrexed in their treatment course.

Although the results of the RCT demonstrate that pemetrexed is beneficial in prolonging disease control and suggest an improvement in OS in patients with non-squamous histology locally advanced or metastatic NSCLC (8), the authors of this report feel that the issue of proper timing of pemetrexed in the patient’s treatment course was not addressed in this RCT. Ciuleanu et al (8) did not report the median time to initiation of second-line therapy in the placebo group. Effective second-line therapies are best delivered prior to a decline in performance status. Unfortunately, the majority of patients with stage IIIB/IV NSCLC do not proceed to second- or third-line therapy (14). Therefore, the benefit seen with switch maintenance with pemetrexed may be due to the timing of chemotherapy and the early introduction of pemetrexed. As the identified RCT did not compare the use of switch maintenance pemetrexed to second-line therapy pemetrexed (i.e., as standard second-line or early second-line), no conclusions can be made regarding the timing of early second-line therapy. Further research is required to determine the best overall treatment strategy for patients with stage IIIB or IV NSCLC.

The rate of grade 3 or 4 adverse events was higher in the pemetrexed arm compared to the placebo arm for neutropenia (3% vs. 0%, p=0.006) and for fatigue (5% vs. <1%, p=0.001) (8). However, there may be a risk of cumulative toxicities incurred from continuous treatment. Many of the patients (57%) in the pemetrexed arm (8) received at least three different chemotherapy regimens (induction, switch maintenance, then second-line) which would have been administered within a shorter time period than in those who receive induction then second-line therapy. This could potentially lead to a decline in performance status, which would preclude the patient from receiving further therapy.

There are select populations of patients with stage IIIB/IV NSCLC who need a more individualized treatment plan but in whom switch maintenance pemetrexed may not be recommended. This group includes those with epidermal growth factor receptor (EGFR) activating mutations-positive tumours. The use of genetic testing for EGFR-activating mutations and the subsequent use of EGFR inhibitors may select out patient populations for a more tailored treatment course. A second group of patients in whom further research is required are those with indolent disease or durable remissions post-platinum-based doublet chemotherapy. These patients are difficult to identify early on and therefore represent a select population in whom switch maintenance pemetrexed may represent overtreatment.

It should be noted that 43% and 57% of patients were in the pemetrexed switch maintenance arm platinum-based therapy with taxanes and non-taxanes, respectively, in the induction phase. As second/third-line therapy in the switch maintenance arm, 22% received docetaxel, 35% an EGFR inhibitor, 9% gemcitabine, and 13% vinorelbine. In the absence of definitive data, a reasonable conclusion is that the use of any of these agents in the second-line setting would be an acceptable option after switch maintenance therapy with pemetrexed.

With the above in mind, it is the opinion of the authors that pemetrexed switch maintenance therapy is a reasonable treatment option for a select population of patients with
non-squamous locally advanced (stage IIIB) or metastatic (stage IV) NSCLC after platinum-based doublet induction chemotherapy. However, such therapy may not be appropriate for all patients. In the opinion of the authors, eligible patients may include those with good performance status (ECOG 0-1) post-induction chemotherapy and with CR or PR or stable disease to induction chemotherapy. There may be a select population of patients with EGFR-activating mutations who may not benefit from this approach. In addition, in those with indolent disease or durable remissions post-platinum-based treatments, switch maintenance pemetrexed may not be beneficial. These patients would represent the select populations for which further research is needed. Clinical discretion should be used until such evidence exists.

CONCLUSIONS

There exists a demonstrated benefit in PFS from the use of pemetrexed switch maintenance in non-squamous histology locally advanced (stage IIIB) or metastatic (stage IV) NSCLC. The opinion of the authors is that pemetrexed switch maintenance therapy is a reasonable treatment option after platinum-based doublet induction chemotherapy for a select population of patients with non-squamous stage IIIB or IV NSCLC. Eligible patients may include those with good performance status (ECOG 0-1) post-induction chemotherapy and with CR or PR or stable disease to induction chemotherapy. Patient populations with EGFR activating mutations-positive tumours and those with indolent disease or durable remissions post-platinum-based treatments represent a unique group to which this recommendation may not be applicable. Further research is required in these patient populations, and clinical discretion and individualized treatment approach would be advised.

ONGOING TRIALS

The United States National Institutes of Health clinical trial registry (ClinicalTrials.gov) was searched for ongoing clinical trials of pemetrexed as a single-agent maintenance chemotherapy in patients with advanced non-squamous NSCLC. Four ongoing trials were identified, details of which can be found in Appendix 2.

CONFLICT OF INTEREST

The authors of this special advice report were asked to disclose potential conflicts of interest relating to the topic of this special advice report. The authors (SC, AH, AR, YU) reported no conflicts of interest.

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Phone: 905-527-4322 ext. 42822    Fax: 905 526-6775   E-mail: ccopgi@mcmaster.ca
REFERENCES

Appendix 1. Literature search strategies.

Ovid MEDLINE
1. pemetrexed:.mp.
2. alimta:.mp.
3. 1 or 2
4. carcinoma, non-small-cell lung/
5. non small cell lung cancer:.mp.
6. NSCLC:.mp.
7. or/4-6
8. 3 and 7
9. meta-analysis as topic/
10. meta analysis.pt.
11. meta analy$.tw.
12. metaanaly$.tw.
13. (systematic adj (review$1 or overview$1)).tw.
14. or/9-13
15. Cochrane.ab.
16. embase.ab.
17. (cinahl or cinhal).ab.
18. science citation index.ab.
19. bids.ab.
20. cancerlit.ab.
21. or/15-20
22. reference list$.ab.
23. bibliography$.ab.
24. hand-search$.ab.
25. relevant journals.ab.
26. manual search$.ab.
27. or/22-26
28. selection criteria.ab.
29. data extraction.ab.
30. 28 or 29
31. review.pt.
32. review literature as topic/
33. 31 or 32
34. 30 and 33
35. comment.pt.
36. letter.pt.
37. editorial.pt.
38. or/35-37
39. 14 or 21 or 27 or 34
40. 39 not 38
41. randomized controlled trials as topic/
42. randomized controlled trial.pt.
43. random allocation/
44. double blind method/
45. single blind method/
46. clinical trials, phase III as topic/
47. clinical trial, phase III.pt.
48. clinical trials, phase II as topic/
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53. placebo$.tw.
54. (allocated adj2 random$).tw.
55. random allocation.tw.
56. randomly allocated.tw.
57. or/41-56
58. case report.tw.
59. letter.pt.
60. historical article.pt.
61. or/58-60
62. 57 not 61
63. 40 or 62
64. practice guideline/
65. practice guideline$.mp.
66. 64 or 65
67. 63 or 66
68. 8 and 67
69. limit 68 to (English language and humans)

EMBASE
1. pemetrexed/
2. pemetrexed:.mp.
3. alimta:.mp.
4. or/1-3
5. exp lung non small cell cancer/
6. non small cell lung cancer:.mp.
7. NSCLC:.mp.
8. or/5-7
9. 4 and 8
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11. ((meta adj analy$) or metaanaly$).tw.
12. (systematic adj (review$1 or overview$1)).tw.
13. or/10-12
14. cancerlit.ab.
15. Cochrane.ab.
16. embase.ab.
17. (cinahl or cinhal).ab.
18. science citation index.ab.
19. bids.ab.
20. or/14-19
21. reference list$.ab.
22. bibliograph$.ab.
23. hand-search$.ab.
24. manual search$.ab.
25. relevant journals.ab.
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27. data extraction.ab.
28. selection criteria.ab.
29. 27 or 28
30. review.pt.
31. 29 and 30
32. letter.pt.
33. editorial.pt.
34. 32 or 33
35. 13 or 20 or 26 or 31
36. 35 not 34
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38. randomization/
39. single blind procedure/
40. double blind procedure/
41. placebo/
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43. rct.tw.
44. random allocation.tw.
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46. allocated randomly.tw.
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49. placebo$.tw.
50. or/37-49
51. case study/
52. case report.tw.
53. abstract report/
54. letter/
55. or/51-54
56. 50 not 55
57. exp practice guideline/
58. practice guideline$.tw.
59. 57 or 58
60. 36 or 56 or 59
61. 9 and 60
62. limit 61 to (human and English language)
### Appendix 2. Ongoing trials.

A phase 3, double-blind, placebo-controlled study of maintenance pemetrexed plus best supportive care versus best supportive care immediately following induction treatment with pemetrexed + cisplatin for advanced nonsquamous non-small cell lung cancer.

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A study of pemetrexed plus carboplatin followed by maintenance pemetrexed vs. paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with advanced NSCLC of nonsquamous histology.

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<th>NCT00948675</th>
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A randomized phase 2 study comparing pemetrexed plus best supportive care with best supportive care as maintenance, following first-line treatment with pemetrexed-cisplatin, in patients with advanced non-squamous non-small cell lung cancer.

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Randomized phase III study of maintenance therapy with bevacizumab, pemetrexed, or a combination of bevacizumab and pemetrexed following carboplatin, paclitaxel and bevacizumab for advanced non-squamous NSCLC.

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