



American Society of Clinical Oncology

Making a world of difference in cancer care

**Clinical Practice Guideline
Update on Chemotherapy for
Stage IV Non-Small Cell Lung
Cancer**

Special Announcement

The US Food and Drug Administration (FDA) approved a new indication for pemetrexed for maintenance therapy in patients with advanced NSCLC on July 2, 2009, when this guideline went to press. The data supporting this change have been recently presented and were outside the scope of the comprehensive data review for this guideline. The recommendation on maintenance therapy in this guideline will be updated pending consideration of recently published relevant data.

Introduction

- The American Society of Clinical Oncology (ASCO) first published evidence-based clinical practice guidelines for the treatment of stages IIB/IV non-small cell lung cancer (NSCLC) in 1997 and updated this in 2003.
- ASCO guidelines are updated at intervals by an Update Committee of the original Expert Panel.
- For the 2009 update, the ASCO Update Committee changed the scope of the guideline to focus on chemotherapy, biologic therapy, and the role of molecular analysis in Stage IV NSCLC, due to the large volume of literature.

Guideline Methodology: Systematic Review

- The panel completed a review and analysis of the medical literature available from January 2002 through July 2008*
- Sources
 - MEDLINE
 - EMBASE
 - ASCO Annual Meeting and IASLC abstracts (search conducted June of 2008)
- Search Dates
 - Aug10-13, 2007; Jan 30, 2008; May 5, 2008; July 29, 2008

*Between August 2008 and May 2009, members of the Update Committee were allowed to nominate studies recently published or presented as an abstract(s) but not identified in the literature or abstract searches.

Limitations of the literature

- Limited numbers of trials enrolling patients with poor performance status (PS \geq 2 based on the ECOG/Zubrod scale, or $<$ 70% on the Karnofsky scale)
- Limited numbers of trials enrolling elderly patients (age $>$ 65 or $>$ 70)
- Lack of phase III data on patients who are being treated with third-line therapy and beyond

Categories of Recommendations

- A. First-line chemotherapy, including duration and schedule of administration
- B. Second-line chemotherapy
- C. Third-line chemotherapy
- D. Molecular analysis

Note: the term chemotherapy, as used here, refers to any anti-cancer drug, regardless of its mechanism of action (i.e. cytotoxic and biologic drugs included), unless otherwise specified.

Clinical Questions New to Update

1. What is the best chemotherapy for treatment of patients with performance status (PS) 2 with stage IV NSCLC?
2. What is the best chemotherapy for treatment of elderly patients with stage IV NSCLC? (elderly usually defined as > 65 or >70 years)
3. Is cisplatin more effective than carboplatin in the first-line treatment of stage IV NSCLC?

Clinical Questions New to Update

4. What are the benefits, with respect to overall survival, progression-free survival, toxicity, and quality of life/symptom relief, in the treatment of stage IV NSCLC with targeted therapies?
5. Is there a role for third-line therapy in the treatment of stage IV NSCLC?
6. For the purposes of prescribing chemotherapy, what is the relevance of molecular analysis of tissue?

2009 Recommendations First-Line Chemotherapy

- Recommendation A1. *Evidence supports the use of chemotherapy in patients with stage IV* non-small cell lung cancer with ECOG/Zubrod performance status 0, 1, and possibly 2.*

*Stage IV as defined by the International Association for the Study of Lung Cancer (IASLC) Lung Cancer Staging Project, for the 7th Edition of the TNM Classification of Malignant Tumors {Goldstraw P, J Thorac Onc , 2007}

2009 Recommendations First-Line Chemotherapy

- Recommendation A2. *In patients with performance status 0 or 1, evidence supports using a combination of two cytotoxic drugs for first-line therapy. Platinum combinations are preferred over nonplatinum combinations because they are superior in response rate, and marginally superior in overall survival. Nonplatinum therapy combinations are reasonable in patients who have contraindications to platinum therapy. Recommendations A8 and A9 address whether to add bevacizumab or cetuximab to first-line cytotoxic therapy.*

2009 Recommendations First-Line Chemotherapy

- Recommendation A3. *Available data support the use of single-agent chemotherapy in patients with a performance status of 2. Data are insufficient to make a recommendation for or against using a combination of two cytotoxic drugs in patients with performance status 2.*
- Recommendation A4. *The evidence does not support the selection of a specific first-line chemotherapy drug or combination based on age alone.*

2009 Recommendations

First-Line Chemotherapy

- Recommendation A5. *The choice of either cisplatin or carboplatin is acceptable. Drugs that may be combined with platinum include the third-generation cytotoxic drugs docetaxel, gemcitabine, irinotecan, paclitaxel, pemetrexed, and vinorelbine. The evidence suggests that cisplatin combinations have a higher response rate than carboplatin and may improve survival when combined with third-generation agents. Carboplatin is less likely to cause nausea, nephrotoxicity, and neurotoxicity than cisplatin, but more likely to cause thrombocytopenia.*

2009 Recommendations First-Line Chemotherapy

- Recommendation A6. *In patients with stage IV NSCLC, first-line cytotoxic chemotherapy should be stopped at disease progression or after four cycles in patients whose disease is not responding to treatment. Two-drug cytotoxic combinations should be administered for no more than six cycles. For patients who have stable disease or who respond to first-line therapy, evidence does not support the continuation of cytotoxic chemotherapy until disease progression, or the initiation of a different chemotherapy prior to disease progression.*

2009 Recommendations First-Line Chemotherapy

- Recommendation A7. *In unselected patients, erlotinib or gefitinib should not be used in combination with cytotoxic chemotherapy as first-line therapy. In unselected patients, evidence is insufficient to recommend single-agent erlotinib or gefitinib as first-line therapy. The first-line use of gefitinib may be recommended for patients with activating EGFR mutations. If EGFR mutation status is negative, or unknown, then cytotoxic chemotherapy is preferred (see Recommendation A2).*

2009 Recommendations First-Line Chemotherapy

- Recommendation A8. *Based on the results of one large phase III randomized controlled trial, the Update Committee recommends the addition of bevacizumab, 15 mg/kg every three weeks, to carboplatin-paclitaxel, except for those patients with squamous cell carcinoma histologic type, brain metastases, clinically significant hemoptysis, inadequate organ function, ECOG performance status >1, therapeutic anticoagulation, clinically significant cardiovascular disease, or medically uncontrolled hypertension. (Based on exclusion criteria for Sandler et al. registration trial) Bevacizumab may be continued, as tolerated, until disease progression.*

2009 Recommendations First-Line Chemotherapy

- Recommendation A9. *Based on the results of one large phase III randomized controlled trial, clinicians may consider the addition of cetuximab to cisplatin-vinorelbine in first-line therapy in patients with an EGFR positive tumor as measured by immunohistochemistry. Cetuximab may be continued, as tolerated, until disease progression.*

2009 Recommendations

Second-Line Chemotherapy

- Recommendation B1. *Docetaxel, erlotinib, gefitinib, or pemetrexed is acceptable as second-line therapy for patients with advanced non-small cell lung cancer with adequate performance status when the disease has progressed during or after first-line, platinum-based therapy.*
- Recommendation B2. *The evidence does not support the selection of a specific second-line chemotherapy drug or combination based on age alone.*

2009 Recommendations Third-Line Chemotherapy

- Recommendation C1. *When disease progresses on or after second-line chemotherapy, treatment with erlotinib may be recommended as third-line therapy for patients with performance status 0 to 3 who have not received prior erlotinib or gefitinib.*
- Recommendation C2. *The data are not sufficient to make a recommendation for or against using a cytotoxic drug as third-line therapy. These patients should consider clinical trials, experimental treatment, and best supportive care.*

2009 Recommendations

Molecular Analysis

- Recommendation D1. *Evidence is insufficient to recommend the routine use of molecular markers to select systemic treatment in patients with metastatic NSCLC.*
- Recommendation D2. *In order to obtain tissue for more accurate histologic classification or for investigational purposes, the Update Committee supports reasonable efforts to obtain more tissue than what is contained in a routine cytology specimen.*
- Guideline reviews evidence on the following molecular markers:
 - EGFR, KRAS, ERCC1, RRM1, VEGF

2009 Recommendations

Future Directions of Research

- Research needed with participants who:
 - are elderly (≥ 65 or ≥ 70)
 - have ECOG Performance Status ≥ 2 (distinguish those with PS ≥ 2 from NSCLC from those impaired by co-morbidities)
- Enrich trial population with participants with tumors with recently discovered prognostic markers and clinical characteristics e.g.:
 - Histology
 - Molecular characteristics
 - Number and time receiving prior therapies
 - With known smoking status

2009 Recommendations Future Directions of Research (cont'd)

- Stratify trials by the prognostic factors listed above
- Treatments which improve only PFS require greater scrutiny for toxicity, side effects, quality of life, and cost effectiveness
- Establish more data on biologic factors of NSCLC in parallel with drug discovery
- Research on strategies to improve patient-clinician communication

Encourage patients to participate in clinical research trials at any time during the course of their disease.

Patient-Physician Communication in NSCLC Treatment

- Research specific to NSCLC has found:
 - Missed opportunities for expressing empathy
 - Observations of blaming words
 - Lack of discussion on prognosis (n.b. approximately 20% of patients may not want discussion of prognostic information)
 - Lack of information-exchange and trust between patients and clinicians of different racial/ethnic backgrounds
 - Intensive training for clinicians can help, as can presence of a caregiver at appointment(s)

Patient-Physician Communication in NSCLC Treatment (cont'd)

- Patients with lung cancer may overestimate the survival benefits of potentially toxic treatment
- Suggested language:
 - “Tell me what you know about your lung cancer?”
 - “How much do you want to know?”
 - “Sounds like what you are telling me is”
 - “It sounds like you were really frightened when you got that news about the cancer.”

Patient-Physician Communication in NSCLC Treatment (cont'd)

- Qualitative statements, e.g. “chances are you will live longer if you take this chemotherapy versus another, or no chemotherapy.”
- Quantitative statements, e.g. “Chemotherapy will improve your chance of being alive in one year from 10-20% up to 30-50%.”
- “Without any chemotherapy, the average person will live about 4 and a half months. With chemotherapy most will live longer and some will live a shorter time. More recent chemotherapy trials have shown that people live about 3 months longer than if they did not get chemotherapy...”
(Continued on next slide)

Patient-Physician Communication in NSCLC Treatment (cont'd)

- *(Continued from previous slide)* “...Even with chemotherapy, the chance of being alive at one year is about 30-50%; the chance of dying within this year is 50-70%.”
- State at least one pessimistic aspect, e.g. “...the chance of dying is....;”
- If asked “can you cure me?” a suggested answer is “No, I can’t, but we have good chances of prolonging your life and keeping you comfortable and we will always be here to help you and your family.”

Guideline Methodology: Update Committee Members

Christopher G. Azzoli, MD, <i>Co-Chair</i>	Memorial-Sloan Kettering Cancer Center
Giuseppe Giaccone, MD, <i>Co-Chair</i>	National Cancer Institute
Reily Smith, <i>Patient Representative</i>	Bakersfield, CA
John R. Strawn, MD, <i>Patient Representative</i>	Houston, TX
Timothy Aliff, MD	Northwest Oncology & Hematology Associates
Sherman Baker, Jr., MD	Virginia Commonwealth University - Massey Cancer Center
Julie Brahmer, MD	Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University
David H. Johnson, MD, <i>Co-Chair 2003 Update and current panelist</i>	Vanderbilt-Ingram Cancer Center
Janessa L. Laskin, MD	British Columbia Cancer Agency

Guideline Methodology: Update Committee Members (cont'd)

Gregory Masters, MD	Helen F. Graham Cancer Center
Daniel Milton, MD	Hematology/Oncology of Indiana, PC
Luke Nordquist, MD	Nebraska Cancer Specialists, PC
William Pao, MD, PhD	Vanderbilt-Ingram Cancer Center
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Steven Piantadosi, MD, PhD	Samuel Oschin Comprehensive Cancer Center Institute
Joan H. Schiller, MD	University of Texas, Southwestern medical Center
Thomas J. Smith, MD	Virginia Commonwealth University - Massey Cancer Center
David Trent, MD, PhD	Virginia Cancer Center

Additional ASCO Resources

- The full text and an abridged version of the guideline, this slide set, and a set of Clinician-Patient Decision Aids can be found at: <http://www.asco.org/guidelines/nsclc>
- A patient guide, “What to Know” about this guideline, is available at <http://www.cancer.net>



ASCO Guidelines

It is important to realize that many management questions have not been comprehensively addressed in randomized trials and guidelines cannot always account for individual variation among patients. A guideline is not intended to supplant physician judgment with respect to particular patients or special clinical situations and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same results. Accordingly, ASCO considers adherence to this guideline to be voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances. In addition, the guideline describes administration of therapies in clinical practice; it cannot be assumed to apply to interventions performed in the context of clinical trials, given that clinical studies are designed to test innovative and novel therapies in a disease and setting for which better therapy is needed. Because guideline development involves a review and synthesis of the latest literature, a practice guideline also serves to identify important questions for further research and those settings in which investigational therapy should be considered.