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Clinical Cases in Advanced Non-Small Cell Lung Cancer

Empowering Practice, Impacting Life

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Clinical Cases in Advanced Non-Small Cell Lung Cancer: Empowering Practice, Impacting Life

A Continuing Education Monograph for Oncology Nurses

Produced and published by OES
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Clinical Cases in Advanced Non-Small Cell Lung Cancer

Empowering Practice, Impacting Life

Educational Objectives

After completing this independent study, the participant will be able to:

- Discuss treatment options and supporting data for advanced non-small cell lung cancer (NSCLC).
- Implement symptom management strategies to enhance the quality of life for patients undergoing treatment for NSCLC.
- Demonstrate optimal nursing roles for active participation in treatment decisions and patient advocacy.

Continuing Education Information

ONS's Approver Unit has approved this independent study for 1.4 contact hours through October 17, 2007. ONS is accredited as an approver of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

ONS's approval of CE credit for this learning program does not imply endorsement of Eli Lilly and Company, nor does ONS assume responsibility for the educational content of this program.

This monograph is an appropriate independent study for oncology nurses interested in learning about the data regarding treatment options for advanced non-small cell lung cancer, the available options for individualized care, and the empowerment of patients and caregivers for playing active roles in treatment decisions.

The post-test for this independent study is also available on the Internet at www.oesweb.com. If you complete the online post-test for CE credit, you are not eligible to receive CE credit for completing the print post-test.

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This unique monograph features illustrations that reflect the dramatic performances offered as part of an OES ancillary event on patient empowerment and non-small cell lung cancer at the 2005 ONS Congress. The character dialogue demonstrates the challenges of patient empowerment. In addition, the monograph provides additional tools for the reader such as a glossary, list of drugs with manufacturers and trade names, and supplemental empowerment bibliography. The appendices contain a useful patient guide to empowerment that can be duplicated for use in practice and questions that can be used in group discussions after individuals have completed the post-test and evaluation.

Introduction

Patient Empowerment

What is empowerment? It is a very important process through which nurses can help assist patients. According to Funnell & Anderson (2003), ***it is the process of helping people to discover and use their innate ability to gain mastery over their disease condition.*** Empowerment has several components including strategies to assist patients in the process and the skills that nurses need to promote it.

There are several strategies that nurses can use:

- Provide patient education to help patients make informed decisions.
- Help patients set self-directed behavioral goals.
- Help patients weigh the costs and the benefits of their treatment.
- Help patients play a very active part in their treatment regimen so that they can be partners in their care.
- Help patients to prevent side effects and/or manage them effectively to achieve the best treatment outcome.

The most important skill a nurse needs is communication. He or she must be able to communicate with patients and ask the appropriate questions. For example, a nurse cannot simply ask a patient, "How do you feel today?" The usual response is, "I'm fine." What does that mean? Nurses must ask targeted questions to get at the source of any kind of problem and help solve it.

Nurses also need to understand the options that the patients want. It is important to appreciate their fears and concerns about their treatment as well as their priorities. Then, nurses can help prioritize the care plan and help them throughout the cancer care continuum.

Empowering patients will help them manage their treatments successfully, play an active role in their care, have optimal quality of life, and, hopefully, meet the goals that they have set for their treatment.

What exactly do patients want? Patients usually want a great deal from their treatment, their nurses, and the healthcare team.

- They want an acceptable quality of life.
- They want to extend life or improve their long-term outcomes so they can achieve particular life goals (see a graduation or see a grandchild born).
- They want to get through their treatment successfully with well-managed side effects, living as normally as possible.
- They want to make informed decisions about their cancer care.

But they want even more from their healthcare team.

- They want its members to be advocates for them.
- They want nurses and doctors to serve as resources.
- They want the team to coordinate their care across different lines of cancer therapy.
- They want to be able to get prompt answers to questions.

Frequently, patients will not ask physicians questions because they feel the physicians are too busy. In that case, a nurse can be the liaison, ask the physician, and get the answers that they need. Patients also want to know about any alternative options and any complementary therapy. Nurses and the healthcare team may want to address enrolment in clinical trials with some patients. Other patients may need help with long-term survivorship issues such as "living beyond the diagnosis," or "finding the new normal for you." They may also need to discuss end-of-life care issues. Overall, they need support.

What is the role of the oncology nurse in patient care? How does a nurse respond to patient needs?

- The nurse advocates for them.
- The nurse educates them.
- The nurse offers them compassion and support.
- The nurse acts as a liaison and a communicator for them.
- The nurse helps walk them through their treatment with the goal of the best possible treatment outcome.

- The nurse acts as a partner in their care.
- The nurse offers them expertise in cancer care and symptom management - quality cancer care.
- The nurse helps to empower the patients to enable them to play very active roles in their care.

Nurses face a number of obstacles, however, in their efforts to empower patients. A patient may not be honest or forthcoming about problems (side effects, financial difficulties, emotional struggles). Another patient may not be compliant with his medication regimen, miss clinic visits, and avoid follow-up. Someone else (and/or her caregiver) may not understand key concepts about her disease and its treatment because of literacy deficits, cultural differences, or linguistic obstacles. Sometimes, a patient's caregiver can present problems by disagreeing with treatment decisions or offering irrelevant information. Nurses may have disagreements with other healthcare professionals about side-effect management, the next steps in therapy, or even stopping therapy. Contemporary insurance restraints sometimes prevent patients from affording or using offered treatment options or require that people use outside labs, complicating coordination. Any of these can pose challenges to patients and their healthcare teams and make it more difficult for nurses to advocate through the cancer care continuum. Nevertheless, the nurse's commitment to patient empowerment will help them to work through the complications and disagreements to achieve the best possible outcome.

One aspect of patient empowerment is the selection of the healthcare team. At the center of the team is the oncologist, a person with appropriate expertise who is a good personality match to the patient. Patients should feel free to seek second opinions, as well. A good nursing team is also critical. Patients should ask, "Let me see where I will be treated. Let me meet the nurses." They should actually see their treatment environment so that they can feel comfortable. In addition, other healthcare workers should be utilized such as dieticians, social workers, and oncology pharmacists. Throughout the team, accurate, open communication is essential.

For more information about empowerment, including efforts in countries other than the U.S. and diseases other than cancer, see the separate bibliography at the back of this monograph.

Advanced Non-Small Cell Lung Cancer

The American Cancer Society estimates that there will be 172,570 new cases of lung cancer in 2005, with over 163,000 deaths. Importantly, there are more deaths from lung cancer each year than from the three other most common cancers (prostate, breast, and colorectal) combined. The incidence of lung cancer in men has decreased over the last 20 years, but the death rate continues to increase in women (Jemal, Murray, et al., 2005; Jemal, Clegg, et al., 2004).

For men, lung cancer increased until around 1980 when its incidence began to decline. This pattern reflects the smoking patterns in men during the 50 years after World War II. Among women, however, the incidence of lung cancer increased. For the period 1975-2000, the death rate for men from lung cancer grew until the early 1990s, then began to decline. Among women, the death rate from lung cancer rose steadily with a slight moderation at the end of the 1990s. Deaths from lung cancer among women have increased 150% since 1980. There are now more deaths from lung cancer in women than from the three major cancers of women combined: breast cancer, uterine cancer and ovarian cancer (Jemal, Clegg, et al., 2004; Jemal, Murray, et al. 2005).

Why has this incidence risen so sharply? First, women's smoking patterns changed dramatically over the last half of the 20th century. After World War II, many more women started smoking, and smoking by women became more socially acceptable. Second, there is evidence that

women are more susceptible to the effects of tobacco smoke. Some studies show that women are more likely to develop lung cancer than men who have the same smoking habits. Recent evidence does not entirely support this contention, finding that women and men have about the same susceptibility to smoking as a cancer trigger (Baldini & Straus, 1997; Risch et al., 1993; Blot & McLaughlin, 2004; Twombly, 2004; Bain et al., 2004). Whatever the proportional risk, the dramatic increase in women's smoking has clearly led to a major increase in women's lung cancer. Nevertheless, women actually do respond better to treatment than men and live longer once they develop lung cancer.

Ninety percent of all lung cancers are related to smoking, and the risks are elevated by several other factors including the number of cigarettes (or quantity of tobacco) smoked. This factor is calculated in pack years, the number of packs smoked per day multiplied by the number of years smoked. (Example: 1.5 packs per day x 30 years = 45 pack years.) The age at which a person started smoking, the product that he/she smoked, the depth of inhalation, and patient gender also influence the development of lung cancer (Davies, Houlihan, & Joyce, 2004; Tyson, 2004b).

Most people with lung cancer present with symptoms. In earlier stages, these symptoms are often ignored because they are the same symptoms associated with a long history of smoking. The most common symptoms are:

- Cough
- Dyspnea
- Hemoptysis
- Chest pain (Tyson, 2004a; Schrump et al., 2004).

There are two major types of lung cancer, non-small cell (NSCLC) and small cell (SCLC). Eighty percent of all lung cancers are NSCLC. Three primary cell types are included in NSCLC: large cell carcinoma, squamous cell carcinoma, and adenocarcinoma. Bronchoalveolar carcinoma, commonly called BAC, represents about 10%-25% of all adenocarcinomas and often has a distinct presentation. It usually presents with diffuse lesions. It is more common in women and in patients who have never smoked, and it tends to be chemotherapy-resistant. It is currently under intense investigation because it seems to respond to targeted therapies better than some other types of NSCLC (NCI, 2004; Schrump et al., 2004; Tyson, 2004b; Laskin, 2004).

The stage of disease is the most important factor in predicting survival in patients with NSCLC. Other factors, particularly performance status at the time of diagnosis, can help predict survival. Performance status is critical because it indicates the patient's ability to tolerate treatment. Other factors include weight loss, gender, and quality of life. Four large meta-analyses of clinical trials done for lung cancer over the last twenty years revealed that survival was also directly related to whether or not patients received chemotherapy for their treatment. Most patients who present with NSCLC are over 70 years of age, but age alone does not seem to be a predictor of survival (NCI, 2004; Tyson, 2004; NCCN, 2005). More than two-thirds of all patients diagnosed with NSCLC present with either stage III (25%), which is considered a locally advanced lung cancer, or with stage IV (45%), metastatic disease (NCI, 2004).

The TNM classification system is used for staging lung cancer. **T** stands for tumor size and location; **N** stands for lymph node involvement, and **M** stands for metastases. In 1997, the classification system for lung cancer was revised to further refine the a and b categories for stages I and II lung cancer. A review of the evidence related to treatment and outcomes prompted this revision. The system was further refined in 2002 (Mountain, 1997; Greene et al., 2002).

TABLE 1. Lung Cancer Staging

Stage	**Ia**	T1, N0, M0
	Ib	T2, N0, M0
	IIa	T1, N1, M0
	IIb	T2, N1, M0 or T3, N0-1, M0
	IIIa	T1-3, N1, M0
	IIIb	Any T4, any N3, M
	IV	Any M1

T = tumor size (T1 < 3 cm, T2 > 3 cm + atelectasis), tumor site (T3 extension to pleura, chest wall, pericardium, or total atelectasis), local involvement (T4 invasion of mediastinum or pleural effusion)
N = lymph node spread N1 bronchopulmonary, N2 (ipsilateral, mediastinal), and N3 (contralateral or supraclavicular)
M = absence (M0) or presence (M1) of **metastases**

Note. From Greene et al., 2002.

TABLE 2. Treatment and Survival, NSCLC by Stage

Stage	Treatment	5-Year Survival, %
I	Surgery	60-70
II	Surgery	30-50
IIIA	Surgery / multimodality regimen	10-30
IIIB	Chemotherapy / radiation	5
IV	Chemotherapy	< 1

Note. From Mountain, 2000; National Cancer Institute, 2004.

The treatments available for NSCLC include all three common modalities: surgery, chemotherapy, and radiation. Stage I and II lung cancers are the most potentially curable, with surgery the most effective treatment. Nevertheless, even these stages have relatively poor long-term survival even when the tumor can be completely surgically resected **(see Table 2)**. Recent evidence suggests that adjuvant chemotherapy in addition to surgery improves long-term survival for this group (Lynch, 2004). In locally advanced lung cancer (stage IIIa), multimodality treatment, including surgical resection and induction or adjuvant chemotherapy and/or radiation, is offered. For stage IIIb lung cancer, surgical resection is not indicated because it does not improve survival. Multimodality therapy at this stage consists of chemotherapy and radiation. For stage IV as well, surgical resection does not improve survival. Chemotherapy is indicated for patients with adequate performance status, and while it will not cure, it can improve symptoms and quality of life in patients. Palliative radiation is also used for stage IV patients to improve symptoms (NCI, 2004; NCCN, 2005).

Cure and improving overall survival are the major goals for the treatment of NSCLC. However, in a disease in which the majority of patients present with advanced disease, there are other important goals as well. Shrinking tumors, stabilizing disease, and prolonging the time between disease progressions are critical factors in these patients. Alleviating symptoms and improving quality of life are essential treatment goals, as well, because they are often much more important to patients than simply living longer: they want to live better. Finally, treatment tolerability and effective management of drug-related adverse events is an important goal in designing treatments for non-small cell lung cancer.

Chemotherapy is effective for symptom relief in advanced NSCLC. During the last decade, an emphasis has been placed on evaluating symptom relief, and quality-of-life measurement is now required for clinical trials. Seven phase III randomized clinical trials for lung cancer have shown that palliation of symptoms was a major outcome and that there was a rate of symptom relief higher than the actual objective response to treatment. Quality-of-life measurements using the FACT-L quality of life assessment for lung cancer (Functional Assessment of Chronic Illness Therapy: facit.org) showed improvement with chemotherapy compared to best supportive care. This trend was evident in trials using vinorelbine, gemcitabine, and cisplatin combination regimens and more recently with HER1/EGFR targeted therapies (Fossella et al., 2000; Fukuoka, et al., 2002; Kelly, et al., 2001; Kosmidis, et al., 2002; Kris, et al., 2002; Massarelli, et al., 2003; Perez-Soler, et al., 2001; Schiller, et al., 2002; Shepherd, et al., 2000; Socinski, et al., 2003).

Results of clinical trials in the last 10-15 years have produced the standardized regimens used for patients with advanced NSCLC as first-line therapy. Platinum-based regimens have proven to provide the best outcomes for patients. These combination regimens include cisplatin and paclitaxel, carboplatin and paclitaxel, cisplatin and vinorelbine, cisplatin and gemcitabine, and cisplatin and docetaxel. The research has shown that patients benefit from chemotherapy within three to four cycles of their treatment plan and that prolonging the therapy beyond that point only leads to increased cumulative toxicity without improving survival time (Socinski, 2003).

Eventually all advanced lung cancer patients progress after initial therapy, and once they do, their survival averages only about three months. Additional research has shown that patients who have good performance status will benefit from second-line therapy **(see Table 3)**. Docetaxel is FDA-approved as a single agent for treatment of patients with advanced NSCLC following failure of a platinum-based regimen. It has shown improved one-year survival and symptom relief over best supportive care, vinorelbine, or ifosfamide (Shepherd, 2003; Fossella, DeVore, et al., 2000; Fossella, Pereira, et al., 2003). Clinical trials with gemcitabine and irinotecan (as single agents and in combination) have not shown results equal to those for docetaxel (Shepherd, 2003). Pemetrexed, a new antifolate chemotherapy previously approved for mesothelioma, received FDA accelerated approval for second-line therapy in advanced NSCLC in late 2004. Its approval was based on a non-inferiority study that demonstrated that it has similar efficacy to docetaxel with fewer adverse events (Eli Lilly and Company, 2004; Shepherd, 2003; Lynch, 2004). It did not show a survival benefit over docetaxel. Finally, two new tyrosine kinase inhibitors (gefitinib and erlotinib) received FDA approval in 2003 and 2004, respectively. Gefitinib received accelerated approval for treatment of advanced NSCLC in the third line, while erlotinib was approved for treatment in the second line and third line. These three agents will be discussed in greater detail later in the monograph.

TABLE 3. FDA-Approved Second-Line and/or Third-Line Therapies Advanced NSCLC

Docetaxel
(Taxotere®, Aventis, Bridgewater, NJ)

Pemetrexed
(Alimta®, Eli Lilly and Company, Indianapolis, IN)

Gefitinib
(Iressa®, AstraZeneca, Wilmington, DE)

Erlotinib
(Tarceva®, Genentech, South San Francisco, CA with Roche and OSI Pharmaceuticals)

Table 4 shows the treatment-survival continuum for advanced NSCLC. For first-line treatment, platinum-based regimens with a new agent can produce a 19%-28% response rate. The one-year survival can be as high as 33%-42%. Second-line treatment with docetaxel can achieve a 5.5%-6.7% response rate, with a one-year survival rate of 19%-21%. Historically, third-line treatment for NSCLC has produced a less than 3% response rate and very few patients live to have a one-year survival. However, some clinical trials for the EGFR-TKI agents have shown response rates of 8.8%-19% and as high as 24%-40% one-year survival rates. **(see references, Table 4).**

TABLE 4. Treatment-Survival Continuum Advanced NSCLC

	Response Rates	Median Survival Rates	One-Year Survival Rates
1st-line treatment	19% - 28%	7.9-10.4 months	33% - 42%
2nd-line treatment	5.5% - 6.7%	5.5-5.9 months	19% - 21%
3rd-line treatment			
Chemotherapies	2.3%	4 months	–
EGFR-TKIs	8.8% - 19%	6.0-8.4 months	24% - 40%

Note. Data from Fossella, et al., 2000; Fukuoka, et al., 2002; Kelly, et al., 2001; Kosmidis, et al., 2002; Kris, et al., 2002; Massarelli, et al., 2003; Perez-Soler, et al., 2001; Schiller, et al., 2002; Shepherd, et al., 2000.

Case 1.

P.M. is a 62-year-old female retired factory worker. She was widowed two years ago. She has an 87-year-old mother with Alzheimer's disease who lives with her. Her 30-year-old, divorced daughter (who is a nursing student) and 8-year-old granddaughter also live with her. She has two married siblings and several nieces and nephews. She is a non-smoker. Eleven months ago, she presented with fatigue and cough. The diagnosis was bronchoalveolar advanced non-small cell lung cancer. The recommended treatment was first-line therapy with carboplatin and gemcitabine. The patient had four cycles of therapy and maintained stable disease on subsequent CT scans. Recent CT scans showed disease progression with an increase in size and number of nodules. The treatment management was changed in response to those CT results, and P.M. was offered second-line therapy with erlotinib.

Erlotinib: Targeting HER1/EGFR

HER1/EGFR (epidermal growth factor receptor - a member of the HER family of cellular receptors) plays a role in many cell processes including at least apoptosis, angiogenesis, proliferation and differentiation, and cell motility and metastasis. A number of targeted therapies have been designed to attack specific parts of the signaling pathways involved in these processes. Some of these work in the extra-cellular domain, particularly monoclonal antibodies. Others, such as the tyrosine kinase inhibitors, work in the intracellular domain (Ciardiello & Tortora, 2002; Herbst, 2004).

Tyrosine kinase inhibitors (TKIs) are oral agents that cross the transmembrane layer and bind at the tyrosine kinase domain inside the cell. These agents are distinctively named with "tinib" to identify them. Gefitinib (Iressa®, AstraZeneca, Wilmington, DE) and erlotinib (Tarceva®, Genentech, South San Francisco, CA, with Roche and OSI Pharmaceuticals) have been approved for the treatment of advanced NSCLC.

Erlotinib is an EGFR-TKI that received FDA approval in late 2004. It is indicated for the treatment of patients with locally advanced or metastatic NSCLC who have progressed after at least one prior chemotherapy regimen. It is orally available, and clinical trials have shown that it is well tolerated. The dose is 150 mg/day. It is a highly selective, potent, and reversible inhibitor of HER1/EGFR tyrosine kinase phosphorylation. Erlotinib competes with

ATP for binding in the intracellular TK domain, blocking signal transduction (Genentech/OSI, 2005).

The pivotal clinical trial leading to FDA approval (BR.21, conducted by the National Cancer Institute of Canada) included 731 patients with advanced NSCLC for whom one or more chemotherapy regimens had failed. Erlotinib demonstrated a survival benefit in essentially all subsets of patients examined including males and females, patients of Asian and non-Asian origins, patients with adenocarcinoma and squamous cell histology, patients with good as well as impaired performance status, and both smokers and non-smokers. Median and one-year survival of the overall population in the BR.21 study was improved by 42.5% (6.7 versus 4.7 months) and 45% (31.2% versus 21.5%), respectively over placebo, and patients were treated with erlotinib for an average of just over 4 months in the study (23% of patients were on therapy for more than 6 months) (Shepherd et al., 2004, 2005).

Certain subsets of patients, including never smokers and patients who had tumors determined to be EGFR positive, were seen to have a large survival benefit in response to treatment with erlotinib. The sub-group of patients who never smoked had a substantial survival benefit with a hazard ratio of 0.42 (hazard ratio is a measure of the risk of death, and a hazard ratio of <1 indicates a survival benefit). The sub-group of smokers also had a survival benefit (hazard ratio = 0.87) despite the fact that this group was also seen to have a 24% higher rate of erlotinib clearance (higher clearance rates lead to lower levels of exposure to drug) (Shepherd et al., 2004, 2005).

In the pivotal NSCLC trial, the most common adverse reactions in patients receiving erlotinib were rash and diarrhea. Grade 3/4 rash and diarrhea occurred in 9% and 6% of erlotinib-treated patients, respectively. About 75% of all patients receiving erlotinib experience rash of any grade. Rash and diarrhea each resulted in discontinuation in 1% of erlotinib-treated patients. Historically, there have been infrequent reports of serious interstitial lung disease (ILD), including fatalities, in patients receiving erlotinib for treatment of NSCLC or other advanced solid tumors. In the pivotal trial in NSCLC, severe pulmonary reactions, including potential cases of ILD, were infrequent (0.8%) and were equally distributed between treatment arms. The overall incidence of ILD in erlotinib-treated patients from all NSCLC studies was approximately 0.7% (Shepherd et al., 2004, 2005) **(see Table 5).**

Continuing analysis of the BR.21 data has also revealed that in the erlotinib-treatment arm, there was a general trend towards improvement of symptoms and quality of life, while in the placebo arm, these deteriorated. At the beginning of the study, symptoms and quality of life were similar for erlotinib patients and the placebo patients. They were experiencing impairments in global quality of life, role, and physical functioning (quality of life meas-

TABLE 5. Erlotinib as a Single Agent in the Second- or Third-Line Setting

	Erlotinib	Placebo	*P*-value
Overall survival	6.7 months	4.7 months	0.001
Progression-free survival	2.23 months	1.84 months	0.001

Note. Data from Shepherd et al., 2004, 2005.

ures), and their symptoms included fatigue, cough, dyspnea, and pain. Patients who received erlotinib had clinically and statistically significantly longer time to deterioration of symptoms: 4.9 vs. 3.68 months for cough (P=0.04), 4.7 vs. 2.89 months for dyspnea (P=0.01), and 2.79 vs. 1.91 months for pain (P=0.02). Erlotinib patients also displayed improvements in these symptoms. Forty-four percent, 34%, and 30% (respectively) of patients reported greater than 10-point improvements on the EORTC QLQ-C30 measures. Thirty-one percent of erlotinib patients reported improvements in physical function vs. 19% of placebo patients (P=0.01), and 35% reported improvements in global quality of life vs. 26% (P=0.01) (Bezjak et al., 2005).

Results from two earlier large, randomized, placebo-controlled clinical trials in first-line advanced NSCLC patients showed no clinical benefit with concurrent administration of erlotinib with doublet platinum-based chemotherapy (carboplatin and paclitaxel or gemcitabine and cisplatin) and its use is not recommended in that setting (TALENT, Gatzemeier et al., 2004; TRIBUTE, Herbst, Prager, et al., 2004).

Research continues to identify factors that would predict sensitivity to EGFR TKIs. Studies so far have suggested that the following patient characteristics may be associated with better outcomes:

- Female gender
- Never-smoker
- Asian ethnicity
- Adenocarcinoma
- BAC
- Genetic mutations in EGFR (Pao, Zakowski, et al., 2004; Patel, Pasche, & Argiris, 2004; Paez et al., 2004; Lynch, Bell, et al., 2004).

Studies have also suggested that rash may be the most consistent correlate of efficacy with TKIs, but not all studies have demonstrated this. Some patients have responded without development of rash (Dancy, 2004).

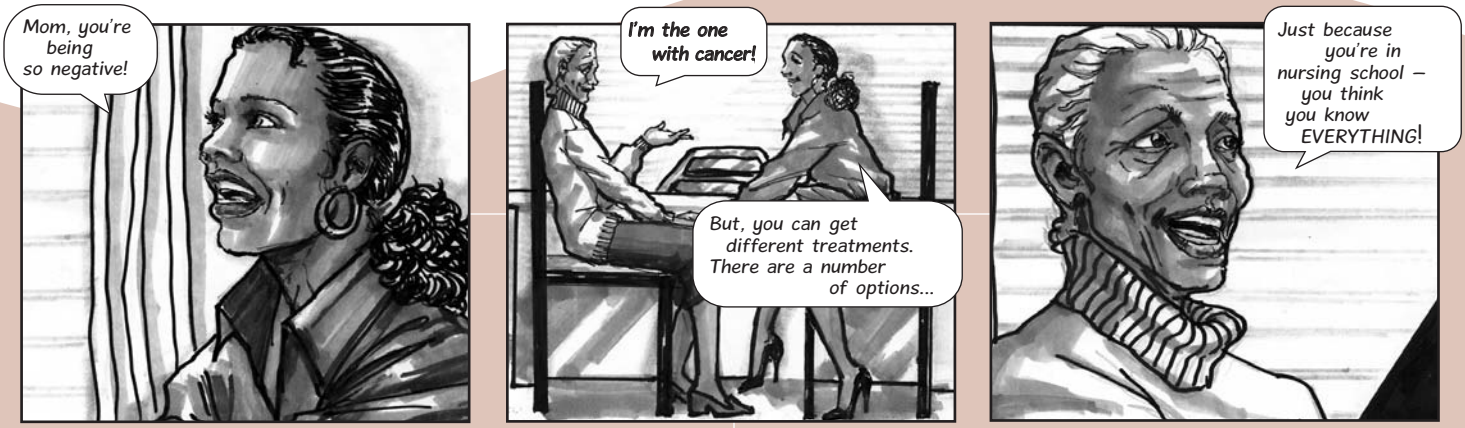
Nursing Considerations

EGFR inhibitors have distinctive treatment side effects that can be expected in a large number of patients. The most universal is rash. Nurses have paramount responsibility for educating their patients about these side effects, symptom management, and dosing issues.

Dosing and Administration

TKIs differ sharply from most chemotherapeutic agents in that they are orally available. Therefore, their administration is home-based, and nurses have a crucial role in informing patients about how to take their medication, when to take it, and what to do in the case of side effects. Because of their unique nature, TKIs do not require special handling or protective measures such as gloves. However, they should be kept away from pets and children. They are provided as coated tablets, and they should be stored at controlled room temperature in their own containers (Genentech, 2004; Pizzo, 2004).

Because erlotinib is a reversible TKI (its effect is temporary, not permanent), it must be taken on a regular schedule: once per day, each day at the same time. If doses are missed, the body concentration of the agent will decline and efficacy will be diminished. It is important that patients, their caregivers, and relevant healthcare providers agree on a monitoring system to insure that the medication is taken every day on time. Some practices use marked pill dispensers, alarm clocks, or calendars to assist patients. Frequent telephone inquiries from nurses



are also often employed to monitor patient compliance. These calls are also often the medium by which clinicians become aware of the development of side effects.

Erlotinib is dosed at 150 mg/day, taken on an empty stomach (two hours after and one hour before a meal). If a dose is missed, it should be taken anytime the same day, between meals. If a dose is completely missed on one day, the drug should be resumed the following day at the regular dose. Two doses should never be taken on the same day. Patients should be advised that they should not eat grapefruit or drink grapefruit juice while taking a TKI because it has been shown to stimulate metabolism of the drug, reducing plasma concentration and perhaps reducing efficacy (Genentech/OSI, 2005).

Important Information for All Patients Receiving Erlotinib

Contact Your Physician If You Experience:

- Severe or persistent diarrhea, nausea, anorexia, or vomiting
- Onset or worsening of unexplained shortness of breath or cough
- Eye irritation

Side Effect Management

Rash

The most distinctive side effect of treatment with EGFR TKIs is rash. It should be described as pustular papular rash, pustular eruption, follicular, or intrafollicular pustular eruptions (Perez-Soler et al., 2005). It is not acne or acneiform.

Clinicians have concluded that the EGFR/HER1 inhibitor rash may actually be a new dermatological entity whose etiology is not entirely known. *It is not an allergic reaction.* It does appear to be the effect of EGFR inhibition in the skin. The rash is usually mild, grade 1 or 2. Grade 3-4 rash is unusual. It has an "above-the-waist" distribution on the head, neck, shoulders, chest, and back. Improvement is usually seen as treatment continues. Only a small percent of patients will require a dose reduction or interruption of drug because of rash. The first signs of rash usually appear within the first week or two of treatment, but it can occur later. It usually resolves gradually during therapy, often by week 4.

There are no clinically tested treatments for the rash. Most over-the-counter preparations are not recommended. Lotions and sunscreen can be used to keep skin more comfortable and to prevent intensification of the symptoms with sun exposure (Shah et al., 2005; Perez-Soler et al., 2005). Other interventions with some utility include:

- Topical corticosteroids, early in therapy, consider specific areas including the face (mild rash)
- Analgesia
- Antibiotics when rash becomes infected; often used prophylactically (Perez-Soler et al., 2005)

Prior to therapy, patients should be warned about the potential to develop rash and instructed **NOT TO STOP TKI THERAPY** if rash does appear. They should contact their healthcare provider for guidance in rash manage-

ment. If at all possible, it is important that patients maintain the maximum dose level in order to sustain efficacy. However, in the case of severe, intolerable rash, dosage reductions or stoppages may become necessary. Erlotinib dosage can be reduced in 50 mg decrements because it is supplied in 25, 100, and 150 mg tablets (Genentech/OSI, 2005).

Other adverse events

- Dermatological:
  1. Itching and erythema
  2. Paronychial inflammation of the lateral nail beds of the fingernails and the toenails
  3. Eyelash and other hair growth can be altered anywhere on the body. Excessive breaking of the hair or thinning of the hair has also occurred. In the case of eyelash growth, patients should be advised not to wear contact lenses (Shah, 2005). All of these effects are relatively uncommon
- Conjunctivitis, keratitis, dry eyes, and eye pain. Artificial tears or lubricants are recommended
- Additionally, liver function tests including AST (aspartate aminotransferase), ALT (alanine aminotransferase), and bilirubin must be monitored, as these can also become elevated. They rarely result in dose reduction or temporary stoppage of drug (Genentech/OSI, 2005)

Diarrhea

Grade 1 diarrhea is most commonly observed. It tends to be transient in nature, and does not usually require dose adjustment or withdrawal. It is easily managed with loperamide. The recommended dose is loperamide 4 mg at first onset, followed by 2 mg q 2-4 hr until diarrhea-free for 12 hr. In the unusual case of grade 3 diarrhea (7 or more episodes in 24 hours), doses of erlotinib should be reduced and not re-escalated. For grade 4 diarrhea, erlotinib may be reduced or stopped if the diarrhea is not responsive to treatment (Shah et al., 2005).

Interstitial lung disease

Interstitial lung disease is estimated to occur in less than 1% of patients taking EGFR TKIs, but retrospective chart reviews in Japanese patients show the incidence in that population to be higher. Symptoms include acute onset of dyspnea, sometimes with cough and fever. It usually occurs within the first month of treatment, and some researchers indicate it occurs by day 18 of treatment. Prompt diagnosis and management is critical in these patients, as approximately 30% of patients who develop ILD will die (Sumpter, 2004; Inoue, 2003).

If a patient presents with acute shortness of breath, or worsening of shortness of breath, erlotinib should be stopped immediately and held until ILD can be ruled out. If ILD is confirmed, do not resume the TKI. High dose corticosteroids and supplemental oxygen are given, and patients are frequently hospitalized and other supportive measures are provided (Baum & Crapo, 2004; Inoue et al., 2003; Michielin et al., 2004).

Drug Interactions

Drug interactions can occur with erlotinib. The medication is highly protein bound, and it is metabolized by the hepatic cytochrome CYP3A4. Drugs that inhibit CYP3A4 can result in high levels of erlotinib in the body, and the high levels can result in greater than normal toxicity. Such drugs include atazanavir (Reyataz®, Bristol-Myers Squibb, Princeton, NJ), clarithromycin (Biaxin®, Abbott Laboratories, N. Chicago, IL), indinavir (Crixivan®, Merck, White House Station, NJ), itraconazole (Sporanox®, Janssen, Toronto, ON), ketoconazole (Nizoral®, McNeil Consumer and Specialty Pharmaceuticals, Ft. Washington, PA), nelfinavir (Viracept®, Pfizer, New York, NY), ritonavir (Norvir®, Abbott Laboratories, N. Chicago, IL), saquinavir (Invirase®, Roche, Nutley, NJ), telithromycin (Ketek®,

Aventis, Kansas City, MO), troleandomycin (TAO®, Pfizer, New York, NY) and voriconazole (VFEND®, Pfizer, New York, NY). In patients receiving these drugs, a lower dose of erlotinib may be needed to prevent toxicity (Saltiel & Marks, 2005).

Some drugs increase the activity of the enzyme CYP3A4 and the elimination of erlotinib may reduce the levels of erlotinib in the body and render the drug ineffective. Drugs that do this include rifampicin (Rifadin®, Aventis, Kansas City, MO), rifabutin (Mycobutin®, Pfizer, New York, NY), rifapentine (Priftin®, Aventis, Kansas City, MO), phenytoin (Dylantin®, Pfizer, New York, NY), carbamazepine (Tegretol®, Novartis, East Hanover, NJ), phenobarbital, and St. John's wort. These drugs should be avoided in patients taking erlotinib, if possible. If alternative drugs are not an option, higher doses of erlotinib may be required (Saltiel & Marks, 2005).

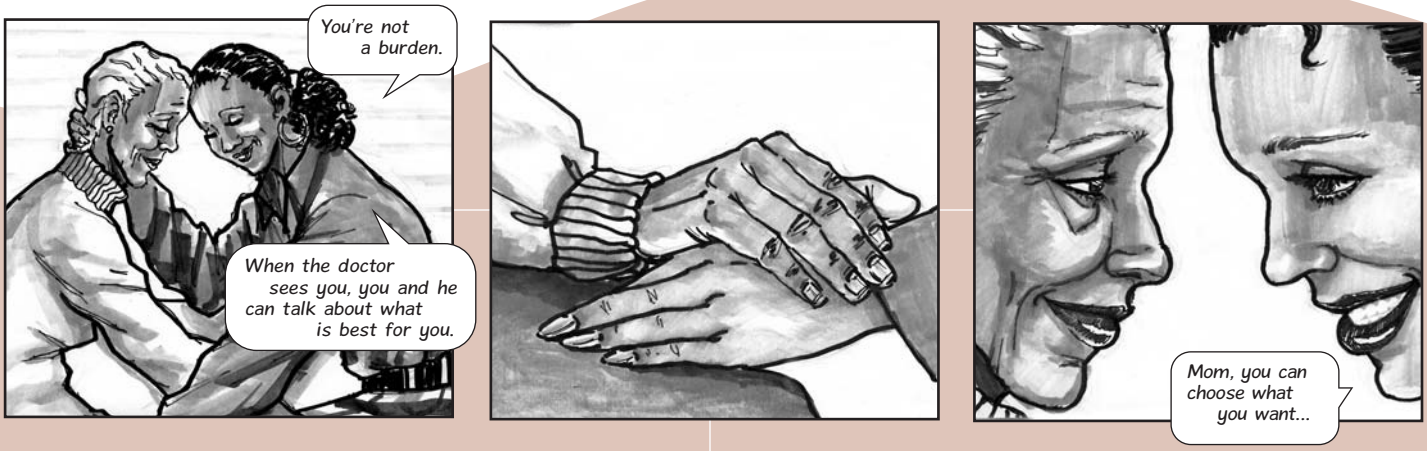
Altered coagulation parameters and/or bleeding have been reported in patients receiving erlotinib either alone or in combination with chemotherapy together with concomitant coumadin-derivative anticoagulants, including warfarin. Patients on coumadin must be monitored carefully. There is a drug/drug interaction between coumadin and erlotinib. The etiology is not entirely clear. Even patients who have been on a stable dose of coumadin for many months need to have their INRs (International Normalized Ratios) monitored more frequently as they may become elevated when treatment is initiated. Sometimes it can be difficult to stabilize the INR when patients are on TKIs.

In summary, rash and diarrhea are the most common side effects seen with erlotinib. Both are usually mild and easily managed, and dose interruption is usually not required. Dose reduction may be required for some. ILD is a potentially serious adverse event that is seen in a small number of patients. Prompt recognition of the problem is critical to patient survival. Drug interactions can occur with drugs that induce or inhibit CYP3A4 and also can occur with coumadin.

Gefitinib

Gefitinib (Iressa™) was the first tyrosine kinase inhibitor (TKI) to receive FDA approval for the treatment of NSCLC. It also targets HER1/EGFR tyrosine kinase. It received accelerated approval as third-line single agent treatment for NSCLC (patients must have taken at least two previous therapeutic regimens) in 2003. The oral dose of gefitinib is 250 mg daily (AstraZeneca, 2005). Response rates are generally between 10% and 15% (Cersosimo, 2004).

The "IDEAL" (IRESSA Dose Evaluation in Advanced Lung Cancer) trials provided the data for the FDA's accelerated provisional approval of gefitinib. IDEAL 1 was conducted mostly outside of the United States, and IDEAL 2 was the United States trial. These phase II trials evaluated gefitinib as monotherapy for advanced NSCLC. Patients were required to have received at least one or two prior chemotherapy regimens (IDEAL 1 and IDEAL 2, respectively). In each trial, patients were randomized to receive either 250 mg of gefitinib or a higher dose, 500 mg. Response rates were 11.8% in IDEAL 2 with the 250 mg dose and slightly less with the 500 mg dose. In IDEAL 1, rates were slightly higher but similar for both doses. The disease control rate (response plus stable disease) was about the same for both trials, between 36% and 51%. Progression free survival (about 2.8 months) and overall



survival (about 7.5 months) were similar in both trials. Rash and diarrhea were the most common side effects (Fukuoka et al., 2002, 2003; Kris et al., 2002, 2003; Cella, 2003; Douillard et al., 2002).

The phase III INTACT 1 and INTACT 2 trials (Iressa NSCLC Trial Assessing Combination Treatment) were designed to explore whether administering gefitinib in combination with chemotherapy would provide a benefit in the first line (Giaccone et al., 2002, 2004; Johnson et al., 2002). The results of these trials showed no differences in survival between the arms in each trial. Patients who received either gefitinib (at either dose) or placebo did about as well. There were also no significant differences in time to worsening of symptoms or progression free survival in the treatment arms of either study. The addition of gefitinib to either chemotherapy combination did not worsen the side effects associated with the regimens, but there was no benefit when gefitinib was added to standard chemotherapy in these patients with advanced NSCLC (Giaccone et al., 2002, 2004; Johnson et al., 2002; Herbst et al., 2004).

The FDA accelerated approval of gefitinib was based on objective response rates and not on survival, as the first trials did not involve comparative placebo arms. The FDA required that AstraZeneca engage in placebo-controlled trials to determine whether gefitinib as a single agent offered a survival benefit. The manufacturer launched the IRESSA Survival Evaluation in Lung Cancer (ISEL) trial and enrolled 1692 patients. Results were announced in December 2004. While there was a statistically significant improvement in tumor shrinkage (objective response rate 8.9%), no statistically significant survival benefit was seen over placebo (median survival 5.6 vs. 5.1 months – gefitinib vs. placebo, P=0.11). The subset of patients with adenocarcinoma also did not experience a statistically significant benefit (median 6.3 vs. 5.4 months – gefitinib vs. placebo, P=0.07). Thus, gefitinib does seem to benefit some patient groups (Asian descent, never smokers), but not the overall population of NSCLC patients (Thatcher, Chang, Parikh, Pemberton, & Archer, 2005; Tyagi, 2005). Another clinical trial testing gefitinib given after chemotherapy and radiation in patients with NSCLC closed early when the gefitinib arm seemed to show worse survival than the arm with standard therapy only (NCI, 2005). In June 2005, the FDA ordered that access to gefitinib be limited only to those patients who had already received it and benefited from the treatment, or to patients in certain clinical trials. The manufacturer is now controlling access to the medication on this basis (FDA, 2005).

Empowering P.M.

P.M. needs assistance in many dimensions of her life. She is at home, she takes care of her mother with Alzheimer's, and her daughter and granddaughter live with her. This multi-generational living situation can lead to stresses during her treatment. She needs to have a good quality of life so that she can handle all of these responsibilities while focusing on her own needs.

P.M. also has a barrier to successful treatment: she lives 150 miles from the cancer center. Can she get to the cancer center? Does she have to depend on rides? Where will she go for laboratory work? When she goes for consultation or treatment, who will take care of her mother or her granddaughter? Will she have to take them with her?

How can P.M. be empowered?

Recall the principles outlined in the introduction:

- Provide patient education to help patients make informed decisions.
- Help patients set self-directed behavioral goals.
- Help patients weigh the costs and the benefits of their treatment.
- Help patients play a very active part in their treatment regimen so that they can be partners in their care.
- Help patients to prevent side effects and/or manage them effectively to achieve the best treatment outcome.

How can these be applied to P.M.'s situation?

1. ***Patient education.*** P.M. needs specific information about erlotinib, its dosing and administration, and its side effects so that she can manage her life effectively. The healthcare team should provide her with detailed instructions about taking the pill at home, once per day, at the same time every day. If she feels that she will have difficulty remembering the regimen's requirements, the team can recruit her daughter to assist in monitoring the medication. In addition, they can provide calendars on which to mark taken doses and frequent home telephone calls to offer support and reminders.

P.M. should be counseled that erlotinib offers her a therapeutic option that is relatively undisruptive to her life: she does not have to travel to the clinic to receive treatments, monitoring can be done largely by telephone (with occasional visits to the clinic), and side effects are usually minor. Possibly the team could offer P.M. the opportunity to stay in touch via the Internet, as well.

P.M. also needs education about the concept of "stable disease" and the range of possible outcomes of treatment with erlotinib. The healthcare team should provide her with oral information, of course, but they should also offer written details as well as directions to various Internet websites where valid information is available.

As part of her education, P.M. could also be informed about the possibility of future enrolment in clinical trials. Some patients find participation in clinical trials to be empowering, as they are working as part of an experimental team to find new, effective therapies.

2. ***Self-directed behavioral goals.*** The healthcare team will need to assist P.M. to set her own goals, but she may need some guidance in determining them. For example, she may need to learn to delegate, giving some responsibility to other people such as her daughter, neighbors, or friends, especially in the care of her mother.

The team's social worker and psychologist can help her accept her current situation and find balance in her life. She will need to re-evaluate her life's priorities. Taking care of her mother and her granddaughter are very important to her, but her disease must take center stage. She needs to take care of herself first and then see how she can get help to fit in all of the other responsibilities. She should not be reluctant to ask for help and seek out people who can help her with her responsibilities. The team can look at local church groups or social clubs to find networks that can support her.

P.M. also needs help in developing a positive outlook on her treatment. She needs considerable reinforcement in her treatment decisions and her ability to carry them out, as well as maintaining hope that the treatment will, in fact, have a good outcome. Although P.M. has not responded

well previously to the idea of participating in a support group, the team may want to propose this concept again. Such groups can often provide just the emotional and practical backup that patients in cancer therapy need. Support groups often also provide essential insight and information for patient families, permitting them to understand the patient's situation better and offer essential assistance.

If P.M. remains reluctant to participate in a group, perhaps a one-on-one situation would be preferable to her. The team could connect her with another patient with whom she could compare experiences and exchange support. Finally, the healthcare team could direct P.M. to various Internet chat rooms and interest groups for additional information and support. If she does not have access to a computer, she can be referred to a cancer information center associated with her treatment center. These are often staffed by nurses or oncology nurses who can counsel patients and/or even perform Internet searches for them.

3. *Costs and benefits of treatment.* The benefits of P.M.'s treatment with erlotinib include a modest side effect profile, potential symptom relief and maintenance of stable disease or even remission, and home-based administration. P.M. certainly fits the profile of those patients most likely to respond to TKI therapy (female, BAC, non-smoker). However, no treatment comes without costs. One of those is side effects, to be discussed below. There are very real financial considerations, as well. How will she pay for her treatment? Can she afford the medicine, which can cost many thousands of dollars, or does she have insurance? What kind of insurance does she have? If she has an 80/20 policy, in which she has a 20% copay, can she afford the 20%? What other financial resources exist to get her the treatment? Are there local foundations or a manufacturer's program to which she can turn?

Does P.M. have to take rides or get transportation the 150 miles to and from the clinic? Does she pay someone? Can she afford that? What resources, such as her church and social groups, can she call on to assist?

4. *Active involvement in care.* If P.M. is assisted to develop coping mechanisms, a support network, and a positive outlook to her therapy, she can be an active partner in her care. The healthcare team needs to be sure that P.M. feels that she has been an intrinsic participant in her treatment decisions and that she has control over the next stages in her life. By offering P.M. home-based therapy, along with a self-monitoring system, the team can give her real authority in her treatment regimen.

5. *Side effect prevention/management.* P.M. must be advised about the potential side effects of erlotinib, especially the rash. She can be informed about the usually mild-to-moderate nature of the rash and receive written suggestions for managing it should it develop. She must be instructed not to stop taking the erlotinib if rash develops, viewing it instead as a possible sign of efficacy. She should also be alerted to potentially severe (and rare) side effects and given an emergency 24-hour number to call if she should develop the signs and symptoms of those more serious side effects.

P.M. has a difficult situation to face. She has progressive non-small cell lung cancer, and she has a complex home life. She feels obligations to her mother, daughter, and granddaughter, and she lives a considerable distance from her cancer clinic. Her healthcare team, with the assistance of her daughter and members of her community, can empower her to make the best of her treatment with erlotinib by teaching her about her treatment, involving her in the treatment decisions and administration, and helping her find the practical and financial assistance she needs. With consistent, positive reinforcement, P.M. can face the next steps with a sense of personal control.

Case 2.

A.M. is a 51-year-old female who works full time. She has been married for 25 years, and her husband travels extensively for work. She has three children: a 21-year-old daughter who is a junior in college, a 17-year-old son who is a senior in high school, and a 14-year-old son who is diagnosed with ADHD. She has a 20-pack-year smoking history (34 years x .6 packs a day = 20.4 pack years). Eight months ago, she presented with vague symptoms including shortness of breath and right shoulder pain. After extensive tests, she was diagnosed with stage IV non-small cell lung cancer. The recommended treatment was docetaxel and carboplatin. The patient had a partial response after four cycles. A CT scan was ordered four months after the last chemotherapy cycle. The CT showed disease progression with several pulmonary nodules present. The patient's treatment management changed in response to the CT results: she was offered second-line treatment with pemetrexed.

Pemetrexed: An Antifolate

Pemetrexed (Alimta®, Eli Lilly and Company, Indianapolis, IN) is an antifolate antimetabolite that disrupts folate-dependent metabolic processes essential for cell replication. There are three types of antimetabolites: purine analogues (6-mercaptopurine and 6-thioguanine), pyrimidine analogues (fluoropyrimidines [5-FU]), and folate antagonists (antifolates). Antimetabolites have chemical structures similar to those needed by cells for normal growth. In chemotherapy, the cell "mistakenly" uses them instead of the essential substances. They prevent DNA reproduction (Goldman & Zhao, 2002). Antimetabolites have the effect of limiting the growth of the most rapidly proliferating cells in the body, such as bone marrow and the lining of the gastric tract. Malignant tumor cells also tend to be rapidly proliferating and are, therefore, attacked by antimetabolites.

Antifolates interfere with binding between natural folate cofactor and biosynthetic enzymes. These include:

- Thymidylate synthase (TS)
- Dihydrofolate reductase (DHFR)
- Gylcinamide ribonucleotide formyl transferase (GARFT)
- Aminoimidazole carboxamide formyl transferase (AICARFT)

Inhibiting these enzymes blocks nucleotide synthesis, interfering in turn with DNA and RNA synthesis. Pemetrexed inhibits GARFT, TS, and DHFR (Goldman & Zhao, 2002; Hanauske, Chen, Paoletti, & Niyikiza, 2001).

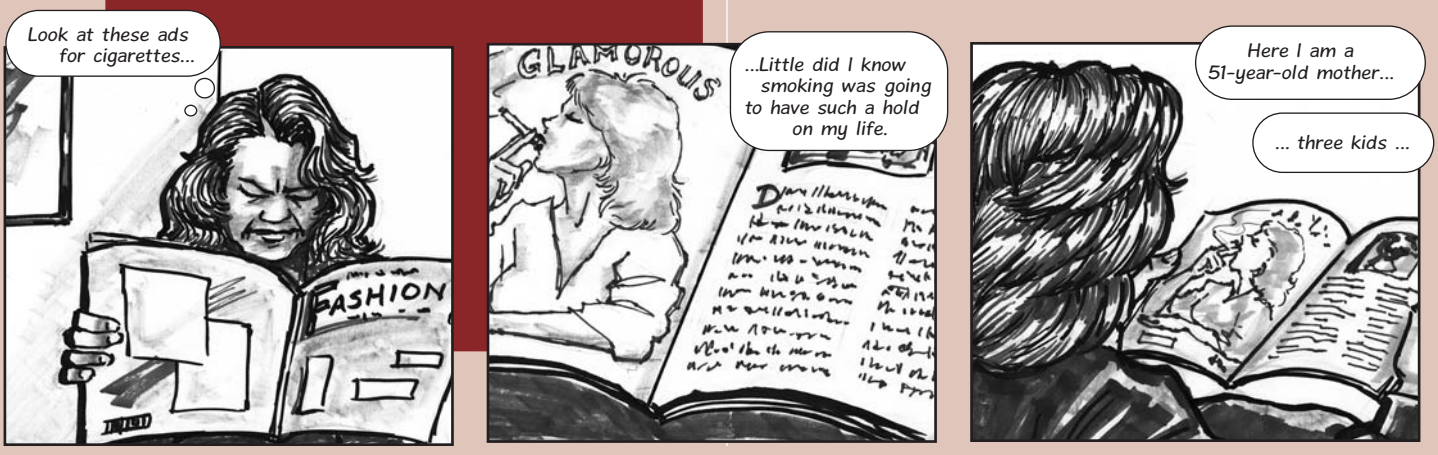
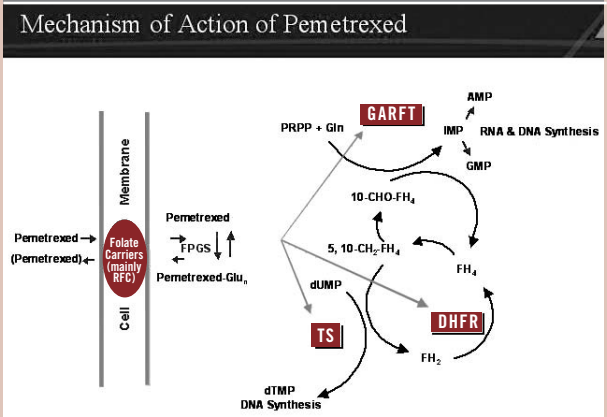


FIGURE 1. Pemetrexed Mechanism of Action



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Pemetrexed is transported into cells by both the reduced folate carrier and membrane folate binding protein transport system. There, it is converted to its polyglutamate form by the enzyme folylpolyglutamate synthetase. This is significant because polyglutamated metabolites have longer intracellular half-lives, resulting in prolonged drug action. The polyglutamation process is a time- and concentration-dependent process within tumor cells, and, to a lesser extent, in normal cells. In other words, it increases with duration of therapy and dose level (Goldman & Zhao, 2002; Hanauske, Chen, Paoletti, & Niyikiza, 2001; Paz-Ares, Bezares, Tabernero, Castellanos, & Cortes-Funes, 2003).

Pemetrexed is FDA-approved for use as a single agent for treating patients with locally advanced or metastatic NSCLC after previous chemotherapy (second line). It was approved in 2004 on the basis of a "surrogate" endpoint, response rate, rather than on survival data, and, to date, there are no controlled trials that demonstrate a clinical benefit such as a survival effect or improvement of disease-related symptoms (Elli Lilly, 2004). However, the pivotal trial that led to its approval did demonstrate that, by comparison to the standard second-line treatment (docetaxel, Taxotere®, Aventis, Bridgewater, NJ), pemetrexed offers equivalent efficacy with a markedly improved side effect profile (Hanna et al., 2004).

The pivotal clinical trial of pemetrexed was a randomized, open-label, phase III study of pemetrexed vs. docetaxel in patients with locally advanced or metastatic NSCLC previously treated with chemotherapy. It was conducted globally in 135 investigational sites in 23 countries. About 21% of the study population was from the U.S. (Hanna et al., 2004).

Five hundred seventy-one patients were randomized between a pemetrexed arm and a docetaxel arm. Patients could be included who had proven NSCLC at stage III or IV, who had previously received only one chemotherapy regimen for advanced disease, who had Eastern Cooperative Oncology Group (ECOG) performance status 0-2, and who had adequate major organ function. Patients were excluded who had symptomatic brain metastases, who had grade 3-4 peripheral neuropathy, who had lost more than 10% of their body weight in the previous 6 weeks, or who had uncontrolled pleural effusions (Hanna et al., 2004). The two arms were well balanced by demographic and stratification characteristics.

Patients in the docetaxel arm received 75 mg/m^2 of docetaxel via 1-hour IV infusion every 3 weeks. In addition, they received dexamethasone 8 mg po bid on days –1, 0, and +1 of each cycle. Patients in the pemetrexed arm received 500 mg/m^2 via 10-minute infusion every 3 weeks. They received folic acid 350-1,000 mg po daily; vitamin B_{12} 1,000 mg IM q 9 weeks; and dexamethasone 4 mg bid on days –1, 0, and +1 (Hanna et al., 2004).

The trial was designed to compare overall survival, tumor response rate, progression-free survival, time to progressive disease, time to response, duration of response, quality of life, and toxicities between the two treatment regimens. Its statistical design was created to demonstrate the non-inferiority of pemetrexed to docetaxel through a number of mathematical tests (Hanna et al., 2004). The tests were intended to reveal whether or not pemetrexed matched the performance of docetaxel and to what extent it either exceeded the expectations for docetaxel or failed to meet them (Cohen, Johnson, Wang, Sridhara, & Pazdur, 2005).

On all efficacy measures, pemetrexed demonstrated no statistically significant difference from docetaxel. Progression-free survival, duration of response, time to response, and time to treatment failure were all directly comparable **(see Table 6)**. In addition, the response, 1-year survival, and stable disease rates were also essentially the same **(see Table 7)** (Hanna et al., 2004).

TABLE 7. Pemetrexed vs. Docetaxel Efficacy Overall

Variable	Pemetrexed (n=283)	Docetaxel (n=288)
Response Rates	9.1%	8.8%
Stable Disease Rates	45.8%	46.4%
1-Year Survival Rates	29.7%	29.7%

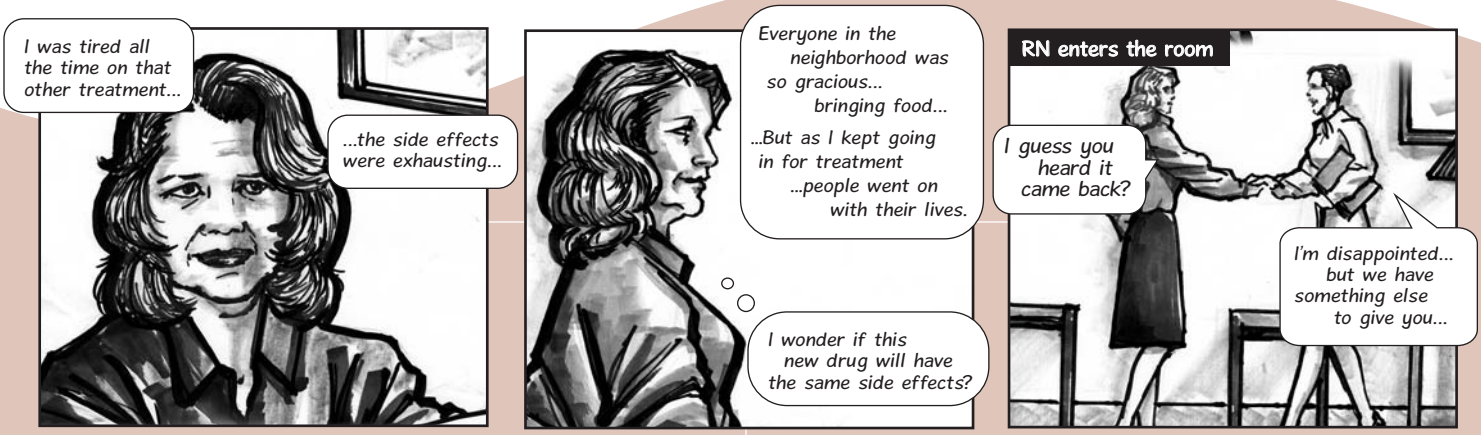
Note. See Hanna et al., 2004, for complete statistical analysis.

Thus, pemetrexed did demonstrate non-inferiority to docetaxel in treating advanced NSCLC. The efficacy results for docetaxel in this trial were comparable to or better than those found in two previous docetaxel trials (Shepherd et al, 2000; Fossella et al., 2000), and the comparative results with pemetrexed may, thus, be viewed as valid. Where pemetrexed demonstrated actual superiority was toxicity. Most non-hematological toxicities were quite similar

TABLE 6. Pemetrexed vs. Docetaxel Efficacy in Time Measures

Variable	Pemetrexed (n=283)	Docetaxel (n=288)	*P*-value
Time of survival (median), months	8.3	7.9	NA
Progression-free survival (median), months	2.9	2.9	.759
Time to progression (median), months	3.4	3.5	.721
Time to treatment failure (median), months	2.3	2.1	.046
Duration of response (median), months	4.6	5.3	.427
Duration of clinical benefit (median), months	5.4	5.2	.450
Time to response	1.7	2.9	.105

Note. See Hanna et al., 2004, for complete statistical analysis.



between the two agents, but alopecia (hair loss) was markedly less in the pemetrexed arm. In that group, 6.4% of patients experienced alopecia, but in the docetaxel group, 37.7% of patients experienced it. Some patients view alopecia as a seriously disfiguring side effect of therapy. There was also a trend toward lower diarrhea rates. The one adverse event in which the pemetrexed group showed a higher rate of occurrence than the docetaxel group was non-symptomatic elevation of ALT. The pemetrexed arm had a 7.9% rate of elevated ALT, while only 1.4% of the docetaxel patients had elevated ALT (Hanna et al., 2004).

Most hematological toxicities, and associated hospitalizations, were sharply lower for the pemetrexed arm than for the docetaxel arm **(see Tables 8 and 9)**.

TABLE 8. **Pemetrexed vs. Docetaxel**
Hematological Toxicities Grades 3-4, % of Patients

	Pemetrexed (n=265)	Docetaxel (n=276)	*P*-value
Neutropenia	5.3	40.2	<0.001
Febrile neutropenia	1.9	12.7	<0.001
Infection with or without grade 3 neutropenia	0	3.3	0.004
Anemia	4.2	4.3	1.00
Thrombocytopenia	2	<1	0.116

Note. See Hanna et al., 2004, for complete statistical analysis.

TABLE 9. **Pemetrexed vs. Docetaxel**
Hospitalizations, Transfusions, and Growth Factor Support
% of Patients

	Pemetrexed (n=265)	Docetaxel (n=276)	*P*-value
> 1 hospitalization due to adverse event	31.7	40.6	0.032
Hospitalization due to febrile neutropenia	1.5	13.4	<0.001
G-SCF/GM-CSF*	2.6	19.2	<0.001
Erythropoietin	6.8	10.1	0.169
Red blood cell transfusions	16.6%	11.6%	0.085

*Granulocyte colony-stimulating factor/granulocyte-macrophage colony-stimulating factor
Note. Hanna et al., 2004.

While anemia and thrombocytopenia (and erythropoietin use and red blood cell transfusions) were similar between the two arms of the trial, neutropenia was dramatically less in the pemetrexed arm. In addition, there was a markedly lower incidence of febrile neutropenia and of infection. Fewer pemetrexed patients were hospitalized due to adverse events, and many fewer were hospitalized for febrile neutropenia. The pemetrexed patients also required far less support with colony-stimulating factors (Hanna et al., 2004).

The researchers concluded that pemetrexed offers a clinically equivalent efficacy to docetaxel in patients with advanced NSCLC with a significantly improved safety profile. The FDA approved pemetrexed for the second-line treatment of advanced NSCLC on the basis of these results in 2004. It was previously approved for the treatment of mesothelioma in combination with cisplatin.

Nursing Considerations

Pemetrexed's positive toxicity profile is possible only with the addition of folic acid, vitamin B_{12}, and dexamethasone to the treatment regimen. Nurses must be prepared to instruct patients in the importance of compliance with the total treatment regimen in order to minimize side effects and optimize outcome.

Dosing and Administration

Pemetrexed is administered as a brief (10-minute) IV infusion in the clinic setting. It cannot be self-administered at home. As noted, it must be accompanied on a specific schedule by folic acid, vitamin B_{12}, and dexamethasone **(see Table 10)**.

TABLE 10. Pemetrexed Dose Schedule

Pemetrexed ***Day 1***	500 mg/m^2 infused over 10 minutes every 21 days
Folic Acid ***Daily***	Daily dose, 350-1000 mg by mouth beginning 1-2 weeks before the first dose of pemetrexed and continuing until 3 weeks after the last dose of pemetrexed
Vitamin B_{12} ***Every 3 cycles***	IM injections, 1000 mg beginning about 1-2 weeks before the first dose of pemetrexed and continuing through treatment every 3 cycles
Dexamethasone ***Days –1, 0, and +1***	4 mg by mouth twice daily on the day before, day of, and day after pemetrexed infusions

Note. Eli Lilly & Company, 2004.

Nurses should follow their institutional guidelines for handling potentially toxic anticancer agents when administering pemetrexed. Gloves are recommended, and if the solution touches the skin, the skin should be washed at once with soap and water. Proper aseptic techniques must be used during the reconstitution and dilution process. Pemetrexed is reconstituted in its original 500 mg vial with 20 mL of 0.9% Sodium Chloride Injection (preservative free) to a concentration of 25 mg/mL. The vial should be gently swirled, not shaken. An additional 100 mL of 0.9% Sodium Chloride Injection is added to the vial after the first reconstitution. This second solution is administered as a 10-minute infusion. Only Sodium Chloride

Injection may be used for reconstitution and dilution, as pemetrexed is not compatible with other diluents. The color of the solution normally varies from colorless to yellow to yellow-green. Reconstituted and diluted pemetrexed solutions are stable for up to 24 hours when stored either under refrigeration or at ambient room temperature. Undiluted pemetrexed should be stored at room temperature (Eli Lilly, 2004).

Safety and Side Effect Management

Myelosuppression is usually the dose limiting toxicity of pemetrexed. It can be expressed as neutropenia, thrombocytopenia, or anemia. Dose reductions may be needed, although for most patients, the vitamin supplementation regimen will prevent severe cases. Skin rash has also been frequently reported, but its incidence and severity are greatly reduced when the patients take dexamethasone as prescribed. The rash is usually cutaneous and desquamation may occur. It may appear between treatments and usually resolves before the next treatment. Patients should call their physicians if the rash is severe and itchy.

Table 11 provides an overview of adverse events experienced by patients with NSCLC in the pemetrexed/docetaxel trial. These patients did receive vitamin supplementation. Only adverse events experienced by more than 10% of patients have been included. The most frequently observed adverse events were fatigue, dyspnea, anorexia, nausea, chest pain, and anemia. The rates of grade 3-4 toxicities were very low, ranging 14% or below (Eli Lilly, 2004).

TABLE 11. Pemetrexed Adverse Events Percentage of Patients

	All grades	Grade 3	Grade 4
Anemia	33	6	2
Leukopenia	13	4	<1
Neutropenia	11	3	2
ALT elevation	10	2	1
Fatigue	87	14	2
Fever	26	1	<1
Edema	19	<1	0
Myalgia	13	2	0
Alopecia	11	NA	NA
Anorexia	62	4	1
Nausea	39	4	0
Constipation	30	0	0
Vomiting	25	2	0
Diarrhea	21	<1	0
Stomatitis	20	1	0
Dyspnea	72	14	4
Chest pain	38	6	<1
Neuropathy	29	2	0
Depression	11	0	<1
Infection/no neutropenia	23	5	<1
Rash	17	0	0

Note. See Hanna et al., 2004; Eli Lilly & Company, 2004.

Precautions

- If a patient has clinically significant third-space fluid (pleural effusions or ascites), clinicians should consider draining the effusion prior to pemetrexed administration. Pemetrexed is structurally related to methotrexate, which has demonstrated increased toxicity in patients with clinically significant fluid collection.
- Because pemetrexed is eliminated by renal excretion, kidney function should be monitored. Patients with a creatinine clearance < 45 mL/min should not receive the drug. Concomitant administration of nephrotoxic drugs could result in delayed clearance of pemetrexed.
- Patient absolute neutrophil count (ANC), platelet counts, and general degree of toxicity should be monitored with each dose of pemetrexed (days 8 and 15). Dose reductions for subsequent cycles are based on nadir ANC, platelet counts, and previous toxicities. Patients should not begin a new cycle of therapy unless the ANC is > 1500 cells/mm^3, the platelet count is > 100,000 cells/ mm^3, and the creatine clearance is > 45 mL/min. Periodic tests should be done to evaluate hepatic toxicity.
- Pemetrexed should not be administered to pregnant women, and patients should be advised against becoming pregnant while receiving pemetrexed. It has shown fetal toxicity and teratogenic activity in laboratory studies. Patients should not breast feed while receiving pemetrexed.
- Patients with mild to moderate renal insufficiency should avoid taking NSAIDs with short elimination half-lives (i.e., ibuprofen and related compounds) for 2 days before, the day of, and 2 days after receiving pemetrexed. Ibuprofen can be administered to patients with normal renal function. All patients taking longer acting NSAIDs (i.e., Cox2 inhibitors) should interrupt dosing for at least 5 days before, the day of, and 2 days following pemetrexed administration. If concomitant administration of NSAIDs is absolutely necessary, patients should be monitored for toxicity, especially myelosuppression and renal and gastrointestinal toxicity (Eli Lilly, 2004).

Dose Reductions

Dosages may be adjusted at the beginning of a new cycle in response to nadir hematologic counts or maximum non-hematologic toxicity. Treatment may also be delayed to allow time for recovery. In the case of ANC < 500/mm^3 and nadir platelets > 50,000/mm^3, dosage may be reduced to 75% of previous level. If nadir platelets fall below 50,000/mm^3, the dose should be reduced 50%. In the case of grade 3-4 non-hematological toxicities or any diarrhea, the dosage should be reduced 25%. Dosage adjustments may be required for patients experiencing hepatic toxicity. For grade 3-4 mucositis, the dosage is reduced 50%. For grades 0-2 neurotoxicity, no dosage alteration is made. For grade 3-4 neurotoxicity, therapy should be stopped. Therapy should also stop if a patient experiences any grade 3-4 toxicity after 2 previous dose reductions (Eli Lilly, 2004).

Empowering A.M.

Just as P.M.'s healthcare team had to develop a specific strategy to empower her, the healthcare team must work to support A.M. in her empowerment. A.M.'s situation is somewhat different from P.M.'s: A.M.'s husband is alive, but he travels extensively for business. A.M. still has two children living at home and one in college. One of her teenage sons, the 14-year-old, has ADHD and is a source of constant concern for her. A.M., too, is experiencing disease progression in her NSCLC, but she faces treatment with a different agent, pemetrexed. Finally, A.M. is burdened by feelings of guilt over her illness. How will the healthcare team help her to manage her situation?

Recall again the principles of patient empowerment outlined in this monograph:

- Provide patient education to help patients make informed decisions.
- Help patients set self-directed behavioral goals.
- Help patients weigh the costs and the benefits of their treatment.
- Help patients play a very active part in their treatment regimen so that they can be partners in their care.
- Help patients to prevent side effects and/or manage them effectively to achieve the best treatment outcome.

How can these be specifically applied to A.M. and her illness?

1. *Patient education.* A.M. should receive very clear directions about her therapy, including the required schedule of vitamins and dexamethasone. A.M. will receive her pemetrexed and vitamin B_{12} in the clinic, but she will be able to take her folic acid and dexamethasone orally at home. She should be reassured that her clinic visits will be brief – the pemetrexed infusion itself takes only 10 minutes – but she will need to come in once a week for blood work. A calendar on which A.M. can keep track of her medications and clinic visits will help her feel in control of her therapy. Fortunately, A.M. lives in close proximity to her cancer center and her older son drives and can help bring her in for her visits.

Like P.M., A.M. needs detailed information about pemetrexed, its side effects and their management, and the potential outcomes of therapy so that she can understand what to expect. She should hear that most patients tolerate pemetrexed well so long as they are compliant with the supplemental regimen. She should also hear why her clinicians have opted for pemetrexed as her second-line therapy instead of docetaxel: less severe side effects.

P.M. may also find Internet sources of information useful.

2. *Self-directed behavioral goals.* A.M.'s guilt and the sense that she is a burden on her family have the potential to severely interfere with her ability to set positive, effective behavioral goals. She needs intensive emotional support, possibly from a psychologist or social worker, to be able to let go of these feelings, accept the situation as it is, and take appropriate action. Even though A.M. was a smoker, the cancer is not her fault. She is entitled to the best possible care and to the love and support of her family, no matter what her past behavior or the illness she may have.

One goal that the team should try to help her set is to get adequate help at home. Her husband, who was absent from the depicted consultation, should be contacted and involved in her treatment and in planning the next steps in their lives together. Perhaps he could arrange to stop or sharply reduce his travel during this treatment period. He could take on some of the responsibility for monitoring the son with ADHD, assisting with homework, medications, and school life. If her husband is unable to limit his travel, the treatment team may want to identify other people in A.M.'s social network (church groups, neighbors, other relatives) who can step in to take on some of the home responsibility. A.M. must be counseled that her requests for assistance are not "burdens" on others, but normal interpersonal exchanges.

Another self-directed goal that would help A.M. take some control of her treatment would be to prepare for her clinic appointments. Especially if she is going to come alone or with her son(s), she needs to learn to write down any questions she may have and be prepared to go

through her list in detail. The more information that A.M. controls, the better prepared she will be to act in her own best interests. A.M. should be encouraged to ask any question that she has and to insist on clarification whenever she does not understand a response.

Finally, A.M. should be encouraged to be completely open and honest with the treatment team about her symptoms, her fears, and her family situation. The team will be able to provide adequate care only if they fully understand A.M. and any problems that might interfere with an optimal outcome.

3. *Costs and benefits of treatment.* Because A.M. experienced unpleasant side effects with her previous therapy, emphasizing the benefits of treatment is especially important for her. The treatment team should emphasize that most patients tolerate treatment with pemetrexed well and that, as long as the patients take their supplements as instructed, side effects are not as intense as those she had previously. Other benefits of pemetrexed treatment include brief clinic visits and the potential of improvement in her clinical symptoms.

Just as with any regimen, there are also costs. In this case, A.M. will have to visit the clinic frequently for either treatment or follow-up laboratory work. Side effects, while usually mild, are possible, and will be discussed below. The treatment team will also need to be sure that A.M. understands her financial situation. What kind of health insurance does her family have? Will there be out-of-pocket costs? If her husband decides to reduce or stop his business travel, how will that influence the family financial picture? What will be the impact on her college-student daughter and/or on her son about to graduate from high school? A.M. must be supported through these discussions. If the overall impact on her family is negative, her guilt may be reinforced, and she will need help in overcoming it.

4. *Active involvement in care.* A.M.'s guilt and sense of being a burden have the potential to prevent her from taking an active role in her treatment decisions and her care. She may feel that she is not worth an investment of time and attention. She may take a passive approach, simply waiting for the doctors and nurses to tell her what to do and not communicating her fears and concerns. The passivity can lead to a "what's the use" attitude, preventing her from directly confronting her situation. The treatment team will have to be especially sensitive to A.M.'s emotional state, repeating important information and reaching out for more information from her. They will need to be encouraging at every point if A.M. is to be empowered to become involved in her care.

A.M. may be a good candidate for a support group. She may also be interested in Internet information groups and/or chat rooms where she can get additional support.

A.M. should also receive information about enrolling in clinical trials. As noted previously, participation in a clinical trial can be very empowering to patients. Given A.M.'s discouraged state, this option might offer her a sense of validation and control over her situation.

5. *Side effect prevention/management.* Given A.M.'s history with therapy and side effects, this is particularly important. The management of the side effects of pemetrexed therapy should be well described, and the appropriate schedule of treatment and supplementation understood. The treatment team will need to provide A.M. with the information she needs to plan her schedule of treatment, monitor her supplements, and adhere to her follow-up appointments. A.M. should receive an emergency contact telephone number in case of unexpected problems.

Like P.M., A.M. is confronted with disease progression of her NSCLC. This can be devastating to patients who have already gone through one round of treatment and side effects, only to learn that the disease has not improved and has actually worsened. A.M.'s mental state is aggravated by her sense of guilt over having "done this to herself." Her treatment team will be challenged to empower her to take control of the situation. They can help her to let go of the guilt, to make arrangements for more help (preferably from her husband) at home, and to learn about her therapy, its supplementation needs, its scheduling, and its potential side effects. They must encourage her by pointing out that this regimen is likely to be less toxic than her previous treatment.

Conclusions

Patient empowerment is one of the most important functions that nurses perform in addition to their vital role in the actual physical care of patients. Empowerment permits patients to develop a sense of control over their disease situation, to adopt positive attitudes about treatment, and to achieve the best possible quality of life. Empowering patients who have recurring or progressing NSCLC can be especially difficult, given the poor prognosis that such patients have. Knowledge is a key to empowerment, and by making sure that such patients have complete, accurate information, that they understand the potential side effects of their treatments and their management, that they have adequate practical support systems at home and in the clinic, and that they have sufficient emotional support, nurses can help to empower them.

P.M. and A.M. each offer challenges to the healthcare team: one lives some distance from the clinic, has extensive family obligations she must manage alone, and will receive erlotinib; the other has a husband who travels extensively, a son who requires intensive attention, and will receive pemetrexed. Certainly nurses see similar patients and handle similar situations everyday. The nurses who help to care for P.M. and A.M. will be able to empower them through their information, referrals, and support.

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Glossary

Adenocarcinoma – a type of carcinoma arising from gland cells

Adenosine triphosphate – nucleotide within the cell, participates in many signaling functions. The energy currency of the cell, transfers energy from chemical bonds to energy absorbing reactions within the cell.

Angiogenesis – creation of new vasculature, esp. in tumors

Antifolate – a substance that inhibits the activity of folic acid. It is also called a folate antagonist

Antimetabolite – a substance that interferes with the metabolic actions within a cell; interferes with cell replication by blocking the replication of DNA

Apoptosis – programmed cell death

Dysregulation – overproduction or under production of growth factors

Efficacy – the ability of an intervention to produce the desired beneficial effect

Epidermal growth factor (EGF) – a growth factor that is important in the development of the cells. It binds to a receptor on the cell surface called the epidermal growth factor receptor (EGFR) to create a growth signal.

Epidermal growth factor receptor – the EGFR is a member of a family of four receptors [EGFR (HER1 or ErbB1), ErbB2 (HER2/neu), ErbB3 (HER3), and ErbB4 (HER4)]. These receptors are large proteins that reside in the cell membrane and each has a specific external ligand binding domain, a transmembrane domain, and an internal domain that has tyrosine kinase enzyme activity.

Folic acid (folate) – a B vitamin (vitamin B9) used by the body to make new cells; works along with vitamin B_{12} and vitamin C to help the body digest and utilize proteins and to synthesize new proteins when they are needed. It is necessary for the production of red blood cells and for the synthesis of DNA.

Glycinamide ribonucleotide formyltransferase inhibitor – blocks DNA synthesis and may prevent tumor growth

Growth factor – A substance that promotes the growth of cells. Growth factors include epidermal growth factor (EGF), fibroblast growth factor (FGF), erythropoietin (EPO), hematopoietic cell growth factor (HCGF), platelet-derived growth factor (PDGF), stem cell factors, and neurotrophins.

Kinases – enzymes that transfer a phosphate group from one molecule to another. Involved in intracellular signaling.

Large cell cancer – type of lung cancer, so called because the cells look large and rounded when viewed under the microscope.

Ligand – A molecule that binds to a receptor protein

Monoclonal antibodies – are produced by a single clone of hybridoma cells and are therefore a single species of antibody molecule.

Phase III study – a study to compare the results of participants taking a new treatment with the results of participants taking the standard treatment. Studies move into phase III only after a treatment seems to work in phases II and I.

Phosphorylation – the addition of a phosphate ion to a protein molecule. Protein kinases act to regulate the activity of proteins by covalently attaching phosphate groups. The addition of this large charged group to the protein will usually result in changes in the target protein's conformation. These conformational changes typically result in changes in the protein's activity (either up or down) or association with other proteins.

Polyglutamate – polymer of glutamic acid

***P*-value** – a measure of probability that a difference between groups during an experiment happened by chance. The lower the *P*-value, the more likely it is that the difference between groups was caused by treatment.

Randomized clinical trial – a study in which the participants are assigned by chance to separate groups that compare different treatment; neither the researchers nor the participants can choose what group. At the time of the trial, it is not known which treatment is best. It is the participant's choice to be in a randomized trial.

Receptor – a specific protein binding site on a cell's surface or interior. When chemicals bind to receptors, various cellular functions are activated or inhibited.

Signal transduction – the biochemical events that conduct the signal of a hormone or growth factor from the cell exterior, through the cell membrane, and into the cytoplasm. This involves a number of molecules, including receptors, proteins, and messengers.

Squamous cell lung cancer – develops from cells that line the airways (bronchi) and is the most common type of lung cancer.

Targeted therapy – the use of an anti-cancer agent to block a specific cellular cycle or pathway with the goal of preventing replication or invasion. The use of targeted therapy increases cell kill rates while preserving normal cells through reduced toxicity.

Thymidylate synthase inhibitor – a drug that blocks DNA synthesis and may prevent tumor cell growth

Tyrosine kinase – an enzyme that catalyzes the phosphorylation of tyrosine residues in proteins with ATP or other nucleotides as phosphate donors

Tyrosine kinase inhibitor (TKI) – A small molecule that interferes with cell communication and growth and may prevent tumor growth; crosses the cell membrane to function inside the cell; prevents tyrosine kinase phosphorylation

Drug Names
and Manufacturers

Atazanavir (Reyataz®, Bristol-Myers Squibb, Princeton, NJ)

Carbamazepine (Tegretol®, Novartis, East Hanover, NJ)

Carboplatin (Paraplatin®, Bristol-Myers Squibb, Princeton, NJ)

Clarithromycin (Biaxin®, Abbott Laboratories, N. Chicago, IL)

Coumadin - generic

Docetaxel (Taxotere®, Aventis, Bridgewater, NJ)

Erlotinib (Tarceva ™, Genentech, San Francisco, CA)

Fluoropyrimidines: fluorouracil 5-FU - generic

Gemcitabine (Gemzar®, Eli Lilly and Company, Indianapolis, IN)

Gefitinib (Iressa® AstraZeneca, Wilmington, DE)

Ibuprofen - generic

Ifosfamide (IFEX®, Bristol-Myers Squibb, Princeton, NJ)

Indinavir (Crixivan®, Merck, White House Station, NJ)

Itraconazole (Sporanox®, Janssen, Toronto, ON)

Ketoconazole (Nizoral®, McNeil Consumer and Specialty Pharmaceuticals, Ft. Washington, PA)

Mercaptopurine - generic

Nelfinavir (Viracept®, Pfizer, New York, NY)

Pemetrexed (Alimta®, Eli Lilly and Company, Indianapolis, IN)

Phenobarbital - generic

Phenytoin (Dylantin®, Pfizer, New York, NY)

Rifabutin (Mycobutin®, Pfizer, New York, NY)

Rifampicin (Rifadin®, Aventis, Kansas City, MO)

Rifapentine (Priftin®, Aventis, Kansas City, MO)

Ritonavir (Norvir®, Abbott Laboratories, N. Chicago, IL)

Saquinavir (Invirase®, Roche, Nutley, NJ)

Telithromycin (Ketek®, Aventis, Kansas City, MO)

Thioguanine - generic

Troleandomycin (TAO®, Pfizer, New York, NY)

Vinorelbine (Navelbine®, GlaxoSmithKline, Research Triangle Park, NC)

Voriconazole (VFEND®, Pfizer, New York, NY)

Warfarin - generic

Appendix A.

A Patient's Guide to Empowerment

Copy these tips and bring them with you to your medical appointments.

Talking With Your Treatment Team:

1. Before going to your doctor's appointment, write down questions when you think of them. Bring the questions with you when you go to the appointment.
2. Be as clear as you can when asking questions or communicating your needs.
3. If you bring books, articles, or information you have printed from the Internet to your appointment, highlight important information you would like to discuss.
4. Take good notes of your conversation with the doctor and/or nurse.
5. Do not be afraid to ask for clarification if you do not understand some of the information that you receive.

Seeking Information:

Your healthcare team can help you make the appropriate decisions to fit your needs and your situation.

1. Take time to think about your options.
2. Seek information in quantities that you can mange.
3. Make sure that you consider all things when looking at your options: treatment schedule, how well it meets your individual treatment goals, drug side-effects, how well the therapy works, and how it will impact your quality of life.
4. Review the information about your options and think of any questions that you need to ask.
5. Take time to discuss your options with those important to you.
6. Take extra time to make sure you are clear about the options, and your decisions.
7. Be patient with yourself.

Seeking Support:

Information and support are widely available to you.

1. Utilize the Internet. However, be cautious about the websites that you choose. Confirm with your healthcare team which websites are reputable.
2. Utilize pharmaceutical company websites, cancer research organizations, hospitals, patient groups, advocacy organizations, and major cancer organizations.
3. Utilize the local library.
4. Take several days to review the information that you find, and ask any appropriate questions or clarify information.
5. Utilize your healthcare professionals: your oncologist and oncology nurse. If you have extensive information to discuss, make an appointment so they are not rushed. This will give you adequate time to review and discuss any questions and personal needs. Take someone with you to the session. If you can't, ask the doctor if you can tape-record them.
6. Utilize your church, synagogue, mosque, or other religious organization's support services for help with transportation, shopping, and more.
7. Seek emotional support or formal counseling to help you deal with feelings of guilt or loss of control.

Choosing Your Healthcare Team:

It is crucial that you find the best healthcare providers possible, and ones that will meet your individual needs.

1. Pick an oncologist who will meet your needs and concerns.
2. Pick an oncologist who will treat you with consideration and respect.
3. Many people choose to seek a second opinion before they make an important, life-changing decision.
4. Learn about the rest of your healthcare team. Your oncology nurses will be the ones that spend the most time with you. Make sure you are comfortable with where you will be treated. Make sure it is a "good fit." Ask to take a tour of the treatment facility. Familiarize yourself with what they have to offer you.
5. Utilize the other members of your healthcare team as well: the dietician, the social worker, and the oncology pharmacist. All of these people are focused on oncology and can help you make the best decisions. They can help provide a smooth treatment continuum.

Other Treatment Considerations:

Medical treatment is very important and is the "backbone" of your treatment plan. Some patients may decide to utilize other things along with their treatment, such as complementary therapy. Others may decide to use "alternative" therapy, which is used "instead of" traditional medical treatment.

1. Vitamins, herbal supplements, and any other over-the-counter (OTC) medications should be discussed with your physician before using.
2. Other complementary therapies may be utilized: acupuncture, heat, massage, cold therapy, prayer, and meditation. These should also be discussed with your physician.

Be as open as possible with your physician and other members of the healthcare team. They can help guide you through treatment and help you to have the best experience possible. Communication is key!

Patient Resources

American Cancer Society
800-ACS-2345 or 404-320-3333
www.cancer.org and **www.ca-journal.org**

American Lung Association
www.lungusa.org

American Society of Clinical Oncology
703-299-0150
www.asco.org

Cancer Care, Inc.,
800-813-HOPE or 212-712-8080
www.cancercare.org

Genentech BioOncology
www.genentech.com

Lilly Oncology
www.lillyoncology.com

National Cancer Institute
800-4CANCER or 800-422-6237 (during working hours). Deaf and hearing impaired callers with TTY equipment 800-332-8615.
www.nci.nih.gov

Appendix B.

Questions for Consideration / Discussion

1. Many new therapeutic agents are oral. What challenges does this pose for the patient and healthcare provider?

2. With pemetrexed's regimen, which includes other medications such as steroids and vitamins, what compliance issues might a nurse see? What strategies can the nurse use to encourage compliance?

3. In reporting clinical trials, symptom relief and quality of life data are now required. Why is this data so valuable?

4. What are the major considerations in the selection of a treatment regimen for a patient with progressive NSCLC?

5. Does your institution have any formal guidelines for empowering patients during their cancer therapy? Why or why not?

6. How have you worked to empower your patients? What specific techniques have you developed?

7. What empowerment techniques will you try based on this monograph?

8. In what aspects of their lives and care do your patients require the most support, especially as they relate to empowerment?

9. How do you use clinical trial data in your routine practice?

10. In advising your patient taking erlotinib, what side effects would it be important for you to discuss? How could they be managed?

11. What instructions would you give your patients taking erlotinib regarding its daily dosage and dosage interruptions?

12. In advising your patient taking pemetrexed, what side effects would it be important for you to discuss? How could they be managed?

Appendix C.

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Continuing Education Post-Test

1. What is the most common side effect of erlotinib?
   A. Elevated liver enzymes
   B. Rash
   C. Chills and fever
   D. Neutropenia

2. Tyrosine kinase inhibitors
   A. Block intracellular signal transduction
   B. Stop receptor dimerization
   C. Prevent ligand binding
   D. Prevent cell division

3. Lung cancer kills more people in the US each year than
   A. Breast cancer
   B. Prostate cancer
   C. Colorectal cancer
   D. All of the above combined

4. First-line chemotherapy for advanced non-small cell lung cancer is usually a combination regimen based on
   A. A monoclonal antibody
   B. A platinum compound
   C. Irinotecan
   D. Fluorouracil

5. Erlotinib can be self-administered because
   A. It is taken as oral tablets and has mild-to moderate side effects.
   B. It is dispensed in self-injection syringes for home use.
   C. It requires few special precautions and can be stored at room temperature.
   D. A and C

6. To date, TKIs have shown no benefit
   A. When administered to non-smokers
   B. When administered to persons of Asian ethnicity
   C. When administered in combination with chemotherapy
   D. When administered to people with BAC

7. Pemetrexed is
   A. An antibiotic
   B. An antifolate antimetabolite
   C. A tyrosine kinase inhibitor
   D. A monoclonal antibody

8. Empowerment includes
   A. Providing information to patients
   B. Requiring patient attendance at support groups
   C. Arranging practical assistance to patients
   D. A and C

9. The dose-limiting toxicity of pemetrexed is
   A. Rash
   B. Neurotoxicity
   C. Myelosuppression
   D. Fatigue

10. Patient premedication with vitamin B_{12}, folic acid, and dexamethasone with pemetrexed is
    A. Optional to reduce side effects
    B. Unneeded
    C. Variable in schedule
    D. Required to limit side effects

11. P.M. will need multiple empowerment strategies, but which of the following will be the most important?
    A. Highlighting information from books and magazines before bringing them to the clinic
    B. Using the local library
    C. Seeking practical assistance to help manage care for her mother
    D. Using the dietician to develop optimal dietary restrictions

12. The following is NOT a barrier to patient empowerment
    A. Written instructions for side effect management
    B. Caregiver interference
    C. Patient distance from the cancer center
    D. Patient feelings of obligation, hopelessness, and/or frustration

Pass it on!

Do you know someone else who wants to learn about non-small cell lung cancer? You **and** your colleagues can read this monograph and earn FREE CE by completing the post-test online at **www.oesweb.com**.

Share the knowledge!

Clinical Cases in Advanced Non-Small Cell Lung Cancer: Empowering Practice, Impacting Life

Post-Test Answer Sheet and Evaluation

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Please circle the letter corresponding to your answer:

1.	A	B	C	D
2.	A	B	C	D
3.	A	B	C	D
4.	A	B	C	D
5.	A	B	C	D
6.	A	B	C	D
7.	A	B	C	D
8.	A	B	C	D
9.	A	B	C	D
10.	A	B	C	D
11.	A	B	C	D
12.	A	B	C	D

To receive continuing education credits for this educational program, you must successfully complete the post-test and submit a completed evaluation form.

Evaluation Form

To assist us in evaluating the effectiveness of the educational design of this program and in making recommendations for future CE activities, please complete the evaluation form by circling the appropriate rating.

Key: 1 = Poor 2 = Fair 3 = Satisfactory 4 = Excellent

How relevant were the objectives to the CE activity's purpose/goals?

The goal of this presentation is provide oncology nurses with knowledge about advanced non-small cell lung cancer, its most current treatment options, and effective treatment planning.

1 2 3 4

To what degree did you meet the following objectives?

Discuss treatment options and supporting data for advanced non-small cell lung cancer (NSCLC).

1 2 3 4

Implement symptom management strategies to enhance the quality of life for patients undergoing treatment for NSCLC.

1 2 3 4

Demonstrate optimal nursing roles for active participation in treatment decisions and patient advocacy.

1 2 3 4

Based on previous experience and knowledge, the level of information in this program was:

1 = Too basic 2 = Appropriate 3 = Too complex

How long did it take you to complete this activity? _____ minutes

Why did you participate in this activity?
A. Amount of continuing education credit hours
B. Importance of topic
C. Quality of faculty
D. Other: _____

How did you obtain this monograph? (Check all that apply)
A. Friend or colleague
B. Conference
C. ONS website
D. Free subscription
E. OES website
F. Other: _____

Will this print piece assist you in providing effective patient care?
A. Yes B. No

How will you modify your practice as a result of this monograph?

_____

What topics would you like to see in the future?

_____

Comments and suggestions for improvements

_____

Was this monograph free of commercial bias? If no, why not?
A. Yes B. No _____