Hope in a Bottle for NSCLC: ERLOTINIB

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Learning Objectives

After completing this activity, the participant should be able to:

- State the importance of mutation status in non-small cell lung cancer
- Describe how mutation status plays a role in clinical practice of NSCLC
- Identify appropriate doses of erlotinib based on diagnosis and presence of potential drug interactions
- Counsel patients on management of the side effects of erlotinib
- State when erlotinib is appropriate in clinical practice

Abstract

Objective: Educate pharmacists and pharmacy technicians on pharmacotherapy and treatment of non-small cell lung cancer (NSCLC) with a focus on the use of erlotinib, including a discussion on its use in NSCLC, important counseling points, and clinical considerations in practice.

Summary: Non-small cell lung cancer is the second most common cancer and is responsible for the most cancer related deaths in the United States. Conventional treatment for non-surgical candidates is chemotherapy which leads to numerous hematologic side effects. Erlotinib is an oral medication that is an alternative to traditional myelosuppressive chemotherapy in select patients with NSCLC. It is a tyrosine kinase inhibitor with activity against mutant epidermal growth factor receptor (EGFR.) These mutations are present in up to fifty percent of Asian and ten percent of Caucasian patients with NSCLC. The most common side effects of erlotinib are rash and diarrhea, both of which can be managed with proper pharmacist counseling and OTC products. Data from the OPTIMAL trial supports that erlotinib offers longer progression-free survival and a better side effect profile than standard chemotherapy in patients with EGFR mutations.

Conclusion: Erlotinib is first-line for patients with advanced, recurrent, or metastatic NSCLC who have known, active, sensitizing EGFR mutations.

Key Words: erlotinib; Tarceva; non-small cell lung cancer; NSCLC
Introduction

Lung cancer is the leading cause of cancer-related death in the United States.\(^1\) According to the National Cancer Institute, over 150,000 people are expected to die from lung and bronchus cancer in 2014.\(^1\) This is more than the estimated number of deaths due to breast, colon and prostate cancer combined.\(^1\) Lung cancer is not only the deadliest cancer, but it is also becoming increasingly more common. Lung cancer is ranked the second most common cancer behind prostate and breast cancer.\(^1\)

There are two distinct types of lung cancer: non-small cell lung cancer and small cell lung cancer\(^2\). Non-small cell lung cancer (NSCLC) is the most prevalent and accounts for nearly 85\% of all cases of lung cancer.\(^2\) Numerous risk factors exist for NSCLC including smoking, exposure to asbestos, radon and arsenic.\(^3\) Although smoking illustrates the most positive correlation with the development of lung cancer, many cases of NSCLC have been diagnosed in both men and women without a history of tobacco smoking.\(^3\) Approximately 19\% of females and 9\% of males who present with lung cancer have no history of tobacco use.\(^4\)

All cancers are staged to determine prognosis. The prognosis of NSCLC varies based on tumor stage at diagnosis.\(^1\) Higher stages are associated with worse prognoses and therefore more aggressive treatment regimens. More favorable 5-year relative survival rates exist for earlier tumor stages. Tumor staging is based on the TNM Classification of Malignant Tumors system.\(^5,6\) (see Table 1)

Every type of cancer has its own classifications of staging while implementing the TMN system. The American Joint Committee on Cancer has defined NSCLC stages as illustrated in Table 2.\(^5\) Stage I is classified as localized. The 5-year relative survival rate
for individuals who are diagnosed with localized non-small cell lung cancer is nearly fifty four percent after resection. The prognoses for patients diagnosed in regional and distant stages are much less optimistic. The 5-year relative survival rates for those groups are twenty seven percent and four percent, respectively. The term “regional” indicates that the cancer has spread to nearby lymph nodes and “distant” indicates the cancer has metastasized. Stage IV is classified as distant.

Treatment of non-small cell lung cancer varies based on several factors. The most important factor is tumor stage with surgery and radiation being the main treatments for early disease (Stage I, II, and potentially IIIa). First-line treatment options for NSCLC differ based on the mutation status, histology of cancer cells and patient comorbidities. Because of this, further molecular diagnostic studies must be performed once pathology results are provided from a biopsy or surgical excision. Several first-line treatment approaches exist based on the results from genetic testing. According to the National Comprehensive Cancer Network guidelines, platinum doublet therapy is preferred for both early-stage and advanced therapy if no gene mutations are identified. In this scenario, four cycles of the chemotherapy are usually given to treat NSCLC. However, if a mutation in exon 19 or 21 of the epidermal growth factor receptor (EGFR) is identified, a tyrosine kinase inhibitor such as erlotinib is recommended as first-line treatment by the NCCN.

Several mutations exist for NSCLC. These key mutations help determine the appropriate therapy for the patient. The epidermal growth factor receptor (EGFR) is a receptor that is present on the surface of epithelial cells. Over expression and/or mutations in EGFR have been discovered in a number of malignancies, including non-
small cell lung cancer. The most common EGFR mutations found in patients with nonsmall cell lung cancer are deletions in exon 19 and a substitution in exon 21. Both of these modifications in the EGFR result in activation of the tyrosine kinase domain, which leads to uncontrolled growth of the cancer cells. According to the NCCN, “these sensitizing mutations are present in about 10% of Caucasian patients with NSCLC and up to 50% of Asian patients.” There is a notable association between exon 19 deletion, exon 21 substitution and response to small molecule tyrosine kinase inhibitors (TKIs). These mutations are known as sensitizing EGFR mutations because they are indicative of therapeutic efficacy towards that drug class. Multiple clinical trials have shown that patients with NSCLC who present with sensitizing EGFR mutations should be treated first-line with TKI. Therefore, it is imperative that patients diagnosed with NSCLC be screened for these pertinent mutations.

**Erlotinib**

Erlotinib is an oral kinase inhibitor indicated in advanced or metastatic non-small cell lung cancer and metastatic pancreatic cancer. Erlotinib reversibly inhibits tyrosine kinase activity of the EGFR. This blockade results in the inhibition of autophosphorylation of tyrosine residues associated with EGFR, which reduces tumor cell signaling, survival and proliferation (see Figure 1). Multiple studies have verified that the response of erlotinib is enhanced when exon 19 deletion or exon 21 L858R substitution for the wild type receptor are present.

The dose of erlotinib varies based on its indication. (See Table 3) Therapy is to be continued until disease progression or unacceptable toxicity occurs.
There are situations when dose reductions or dose increases are indicated (see Table 4). If a patient stops smoking during treatment, the dose of erlotinib must be immediately reduced to the therapeutic dose.¹⁰ “Concomitant use of [erlotinib] and proton pump inhibitors should be avoided. If treatment with an H₂-receptor antagonist such as ranitidine is required, erlotinib must be taken 10 hours after the H₂-receptor antagonist dosing and at least two hours before the next dose of the H₂-receptor antagonist.”¹⁰ This is necessary because H₂-antagonists may decrease the serum concentration of TKIs.⁹ All antacids present with this risk; therefore administration of products such as calcium carbonate and erlotinib should be separated by several hours.⁹

The most common side effects of erlotinib are rash and diarrhea. It is imperative that the patient does not discontinue the medication at the onset of rash or diarrhea unless instructed to do so by his health care provider. Pharmacists must properly counsel on these side effects because it is thought to be related to the efficacy of the kinase inhibitor (see Role of the Pharmacist). Other side effects include shortness of breath, fatigue, and cough.⁹,¹⁰ Erlotinib is classified as having minimal emetic potential (<10%) – however nausea, vomiting and diarrhea are still possible side effects of the medication.⁹ Patients should be advised to contact their health care provider if they experience serious or ongoing gastrointestinal upset (including nausea, vomiting, diarrhea and loss of appetite), new or worsening shortness of breath including cough, eye irritation, new or worsening blistering or peeling of the skin or any changes in smoking habits.⁹,¹⁰
There are currently no contraindications to the use of erlotinib. Warnings and precautions exist for the following conditions: interstitial lung disease (ILD), renal failure, hepatotoxicity with or without hepatic impairment, gastrointestinal perforation, bullous and exfoliative skin disorders, myocardial infarction/ischemia (MI), cerebrovascular accident (CVA), microangiopathic hemolytic anemia (MAHA) with thrombocytopenia, ocular disorders, hemorrhage in patients taking warfarin, and embryo-fetal toxicity. It is recommended to discontinue the use of erlotinib in patients who develop interstitial lung disease, severe renal failure, severe hepatotoxicity, gastrointestinal perforations, bullous and exfoliative skin disorders and ocular disorders. The risk of MI, CVA and MAHA are increased in patients with pancreatic cancer; therefore, the risks and benefits on the use of erlotinib in this patient population should be discussed with the patient and their medical oncologist. Erlotinib is in pregnancy category D (positive evidence of human fetal risk but potential benefits may warrant use). Women of childbearing age must be advised of the fetal risks and counseled on the use of effective contraception. Erlotinib is to be taken on an empty stomach, one hour before or two hours after a meal. Grapefruit juice should be avoided due to a potential drug interaction via cytochrome 3A4 metabolism.

The tablets should be stored at room temperature of 25C (77F); when transporting erlotinib, it should be stored between 15C and 30C (59F and 86F). This novel kinase inhibitor is classified as a hazardous agent. Appropriate storage and handling measures must be taken in accordance to the National Institute for Occupational Safety and Health (NIOSH). Erlotinib is recommended to be stored in a glass, polyethylene or polypropylene container. The containers must be clearly labeled.
and leak-free. NIOSH requires that “antineoplastic (cytotoxic) wastes must be packed directly, ready for incineration, into color-coded, secure, labeled, leak-proof containers sufficiently robust to withstand handling without breaking, bursting or leaking.” Most cancer centers or hospitals will dispose of the unused medications for patients if they do not have access to such containers.

A suspension can be prepared for oral or feeding tube administration. The preparer will dissolve the number of tablets to make the prescribed dose into 100mL of water, then rinse the container adequately to ensure 100% of the medication has been incorporated into preparation. All compounding materials and equipment should be treated as hazardous and disposed of properly. The average cost of 30 tablets of 150mg erlotinib is $7,454.44 based on average wholesale price (AWP) and/or average of the AWP (AAWP) from Genetech USA, Inc. This product is available under the brand name Tarceva ®.

The cobas ® Mutation Test is an FDA approved medical device used to determine patient’s eligibility for Tarceva (erlotinib). It is recommended that all patients diagnosed with non-small cell lung cancer provide a biopsy to undergo the cobas ® Mutation Test and there are no current contraindications to its use. The automated molecular assay examines the patient's tumor biopsy. The results will indicate whether or not the two pertinent EGFR mutations are present in the NSCLC cells: exon 19 deletion or exon 21 substitution. Presence of either mutation indicates a high likelihood of response to erlotinib.

Role of the Pharmacist
Proper patient counseling on the use of erlotinib is essential. The development of a skin rash is likely to occur with the use of erlotinib. On average, 49% to 85% of patients on erlotinib develop a rash on their face, upper chest and back.\textsuperscript{9} In most other medication classes, the onset of a rash may indicate a serious allergic reaction. The onset of skin reactions while on erlotinib is a positive occurrence and may be indicative of treatment response. It is essential that pharmacists counsel patients on this and how to manage the reaction because it is likely to cause the patient to stop taking the medication. In many cases, the skin reaction is erythematous, maculopapular and may resemble follicular pustules seen in acne.\textsuperscript{10} The rash is not acne and should not be treated as such. Products such as benzyl peroxide (commonly used to treat acne) will worsen the rash associated with erlotinib.\textsuperscript{10} There are multiple options available to minimize the burden of erlotinib-associated rash. First, proper skin hygiene should be initiated including cleansing the skin with mild soap products, moisturizing with alcohol-free products, and protecting skin from damage with sunscreen.\textsuperscript{10} Sunscreen with SPF of 30 or higher should be used daily. If a rash develops, the patient should not scratch the affected areas. This can spread and/or worsen the reaction. Taking erlotinib with food can increase the likelihood of rash development.\textsuperscript{10} Proper administration on an empty stomach can help minimize the onset of skin rash. If the rash persists, the patient should contact their oncologist. Medical oncologists can prescribe prescription products to better manage erlotinib-associated rash. Corticosteroids and anti-inflammatory antibiotics can help alleviate symptoms of the skin reaction. The oncologist can also withhold erlotinib therapy until symptoms have resolved in severe cases, and reintroduce the TKI at a reduced dose.
Diarrhea is another common side effect of erlotinib that patients endure. The side effect of erlotinib can generally be managed with over-the-counter products such as loperamide. The onset of diarrhea is common in the first month of erlotinib therapy.\textsuperscript{10} It is important to counsel the patient on non-pharmacologic treatment of diarrhea such as proper hydration (at least 8 glasses of a non-caffeinated beverage daily), eat mild foods, eat multiple small meals and snacks throughout the day rather than three large meals\textsuperscript{10}. Recommend that the patient limit caffeine, tea, hot beverages, spicy foods, foods high in fiber and dairy products\textsuperscript{10}. The patient should be aware of signs and symptoms of dehydration and is encouraged to keep a log of the number of occurrences of diarrhea per day, weight loss, food and water consumed daily.\textsuperscript{10} The patient should be advised to see their oncologist if diarrhea persists despite self-care measures.

Regular liver function tests, renal function tests and hydration status should be assessed while a patient is on erlotinib.\textsuperscript{9} Elevated ALT was a common side effect of erlotinib in the OPTIMAL trial (see Early Implications of Clinical Controversy).\textsuperscript{7} Liver function should be assessed at baseline and periodically during treatment.\textsuperscript{9} Renal function tests should be monitored in patients who are at risk of dehydration.\textsuperscript{9}

Pharmacists are patient advocates and therefore they should be the person to ensure adequate insurance coverage of the medication. Erlotinib should be covered if the patient tests positive for NSCLC whose tumor presents with an exon 19 deletion or exon 21 substitution in the EGFR. It is important to note that all insurance policies differ, but proper coverage must be verified prior to the start of treatment due to its high cost.

Pharmacists also must inform their staff of proper storage and handling of the product. Erlotinib is classified as a hazardous substance and must be handled as such
due to antineoplastic classification and reproductive toxicities. Proper MSDS (material safety data sheet) sheets must be available to employees and training should be offered. Several medication safety issues exist with antineoplastics. Therefore, proper labels and storage must be implemented in the pharmacy. In addition, erlotinib is classified as a high alert medication, defined by the ISMP as a drug class that has heightened risk of causing significant patient harm when used in error.\

Clinical Implications or Early Controversy

Early clinical trials failed to show a survival benefit of erlotinib when used in NSCLC. These primary trials such as the TALENT trial and TRIBUTE trial did not select patients based on EGFR mutation status.\textsuperscript{13, 14} Multiple phase-3, randomized trials have been performed since the sensitizing EGFR mutations were discovered. The first head-to-head phase-3 prospective study analyzing erlotinib in patients with positive EGFR mutation status was the OPTIMAL trial. The OPTIMAL trial concluded that patients with advanced EGFR-positive NSCLC who were treated with erlotinib had a longer survival period with tolerable side effects compared to those treated with conventional therapy (gemcitabine plus carboplatin).\textsuperscript{7} OPTIMAL was a multicenter, open-label, randomized phase-3 study performed in China.\textsuperscript{7} It reinforced the importance of proper routine EGFR mutation testing in advanced non-small cell lung cancer. Neutropenia, thrombocytopenia, nausea/vomiting, and fatigue were all significantly more pronounced in the chemotherapy group.\textsuperscript{7} Rash and increased alanine aminotransferase (ALT) were the two most common adverse effects within the erlotinib group.\textsuperscript{7} The National Comprehensive Cancer Network (NCCN) Guidelines reflect the conclusion of the
OPTIMAL trial. Erlotinib is first-line for patients with “advanced, recurrent, or metastatic NSCLC who have known, active, sensitizing EGFR mutations.”

References


Table 16: TNM Staging System for Malignant Tumors

<table>
<thead>
<tr>
<th>Classification</th>
<th>Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T</strong></td>
<td></td>
</tr>
<tr>
<td>TX</td>
<td>Tumor cannot be measured</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td><em>in-situ</em> cancer (pre-cancer)</td>
</tr>
<tr>
<td>T1-4</td>
<td>Numbers describe tumor size and/or amount it has spread to nearby tissues; the higher the number, the larger the size/more the tumor has spread</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N</th>
<th>Node</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Nearby lymph node cannot be measured</td>
</tr>
<tr>
<td>N0</td>
<td>Nearby lymph nodes do not contain cancer</td>
</tr>
<tr>
<td>N1-3</td>
<td>Numbers describe the size, location, and number of lymph nodes affected; the higher the number, the more the lymph nodes involved</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>Metastasis cannot be evaluated</td>
</tr>
<tr>
<td>M0</td>
<td>No distant cancer was found</td>
</tr>
<tr>
<td>M1</td>
<td>Cancer has metastasized to distant sites</td>
</tr>
</tbody>
</table>
Table 26: NSCLC classifications and prognostic groups with respect to TNM system

<table>
<thead>
<tr>
<th>Anatomical stage/prognostic groups</th>
<th>Occult Carcinoma</th>
<th>Stage 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX N0 M0</td>
<td>Tis N0 M0</td>
<td></td>
</tr>
<tr>
<td>Stage IA</td>
<td>T1a N0 M0</td>
<td>T1b N0 M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T2a N0 M0</td>
<td>T2b N0 M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T1a N1 M0</td>
<td>T2a N1 M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T3 N0 M0</td>
<td>T2b N1 M0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T1a N2 M0</td>
<td>T3 N1 M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T2a N2 M0</td>
<td>T3 N2 M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T Any N M1a</td>
<td>Any T Any N M1b</td>
</tr>
</tbody>
</table>

Figure 115: Erlotinib mechanism of action

EGFR signal
EGFR signals tell cancer cells to grow and multiply out of control.
Tarceva can slow or block these signals. This may cause cancer cells to die. It also affects healthy cells.
Table 3: Erlotinib Dosing

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-small cell lung cancer</strong></td>
<td></td>
</tr>
<tr>
<td>• First-line in patients with EGFR exon 19 deletion of exon 21 substitution</td>
<td>150mg by mouth, once daily</td>
</tr>
<tr>
<td>• Maintenance therapy</td>
<td></td>
</tr>
<tr>
<td>• Refractory</td>
<td></td>
</tr>
<tr>
<td><strong>Pancreatic cancer</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>100 mg by mouth, once daily (in combination with gemcitabine)</td>
</tr>
<tr>
<td>Scenario</td>
<td>Dose adjustment</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>------------------------------------------------------</td>
</tr>
<tr>
<td>Erlotinib is used in combination with both a CYP3A4 inhibitor and CYP1A2 inhibitor</td>
<td>Decrease erlotinib by 50mg</td>
</tr>
<tr>
<td>Severe reaction occurs when erlotinib is used in combination with a strong CYP3A4 inhibitor (clarithromycin, atazanavir, ketoconazole)</td>
<td>Decrease erlotinib by 50mg</td>
</tr>
<tr>
<td>Erlotinib is used in combination with CYP3A4 inducer (rifampin, carbamazepine, phenobarbital, St. John’s Wort)</td>
<td>Increase erlotinib by 50mg at 2-week intervals to a maximum of 450mg</td>
</tr>
<tr>
<td>Concurrent cigarette smoking</td>
<td>Increase erlotinib by 50mg at 2-week intervals to a maximum of 300mg</td>
</tr>
</tbody>
</table>
Self-assessment questions:

1. Which of the following is the most appropriate dose of erlotinib for NSCLC?
   a. 150 mg by mouth twice daily with meals
      i. Dosing should be once daily on an empty stomach
   b. 150 mg by mouth once daily with meals
      i. Administration must be on an empty stomach
   c. 150 mg by mouth once daily one hour before or two hours after a meal**
   d. 150 mg by mouth twice daily one hour before or two hours after a meal
      i. Dosing should be once daily on an empty stomach

2. Which of the following is the most accurate conclusion of the OPTIMAL trial?
   a. Erlotinib was superior to conventional therapy in both EGFR-positive and EGFR-negative patients with NSCLC
      i. The OPTIMAL trial only included EGFR-positive patients
   b. Erlotinib was superior to conventional therapy in EGFR-positive patients with NSCLC**
   c. Erlotinib was inferior to conventional therapy in both EGFR-positive and EGFR-negative patients with NSCLC
      i. The OPTIMAL trial only included EGFR-positive patients
   d. Erlotinib was inferior to conventional therapy in EGFR-positive patients with NSCLC
      i. The OPTIMAL trial concluded that erlotinib was superior to conventional therapy for EGFR-positive patients

3. A 36 year-old female was recently diagnosed with stage IV metastatic NSCLC. Tumor tissue was tested for EGFR and ALK mutation and found to be negative. She is treatment naïve and has no known drug allergies. What dose of erlotinib should be started in this patient?
   a. 150mg by mouth once daily one hour before or two hours after a meal
      i. Erlotinib is only indicated in patients with positive EGFR mutation status
   b. 150mg by mouth once daily with meals
      i. Erlotinib is only indicated in patients with positive EGFR mutation status
   c. It is not appropriate because no ALK mutation was identified
      i. Erlotinib is only indicated in patients with positive EGFR mutation status
   d. It is not appropriate because no EGFR mutation was identified**

4. Which of the following side effects are the least likely to occur in patients on erlotinib?
   a. Diarrhea
      i. Rash and diarrhea are common side effects of erlotinib
   b. Rash
      i. Rash and diarrhea are common side effects of erlotinib
c. Thrombocytopenia**
   i. Thrombocytopenia is a common side effect of conventional chemotherapy, not erlotinib

d. Nausea
   i. Nausea is a side effect of erlotinib even though the medication does have a low emetic potential.

5. A 47-year-old male was diagnosed with metastatic NSCLC three weeks ago. The tumor tissue was found to be positive for EGFR mutation (exon 19 deletion). Erlotinib 150mg daily was started at that time. The patient presents to your pharmacy today and complains of worsening rash on his face, upper back and shoulders. You notice that the rash resembles acne. What is the most appropriate recommendation for the patient?
   a. Start an OTC product such as benzyl peroxide or salicylic acid
      i. Products such as these will worsen the rash
   b. Start cleansing his skin with a mild soap and moisturizing with alcohol-free products**
   c. Discontinue erlotinib because patient is experiencing a hypersensitivity reaction
      i. A rash is expected to occur with erlotinib use and may be indicative of treatment response
   d. Take erlotinib with food to decrease the severity of the rash
      i. Taking erlotinib with food will increase the severity of the rash; Erlotinib should be taken once daily on an empty stomach

6. A 58-year-old man with refractory NSCLC presents to your pharmacy. He has been on erlotinib 300mg for 9 weeks with adequate response. Patient denies any side effects. His past medical history includes hypertension x 10 years, dyslipidemia x 5 years, and smoking 2ppd x 30 years. His medications include lisinopril 20mg and atorvastatin 10mg. The patient states he recently quit smoking and has not smoked a cigarette in 2 weeks. The dose of erlotinib:
   a. Must be immediately reduced to therapeutic dose of 150mg daily**
   b. Must be increased by 50mg in 2-week increments to a maximum of 400mg daily
      i. The dose of erlotinib should be increased by 50mg in 2-week increments to a maximum 300mg in patients who smoke when they start erlotinib
   c. Must be reduced by 50mg in 2-week increments to 100mg daily
      i. Erlotinib must be immediately reduced to therapeutic dose of 150mg once daily on an empty stomach
   d. Is not affected by cigarette smoking

7. A 71-year-old man with stage IV NSCLC presents to your pharmacy. His past medical history includes type-2 diabetes, dyslipidemia and hypertension. His current medications include erlotinib (x 3 weeks), metformin (x 10 years), atorvastatin (x 8 years) and lisinopril (x 12 years). The patient has dry mucus
membranes, is lethargic and thirsty. Patient states that he has had 6 episodes of diarrhea in the last 48 hours. What is the least appropriate recommendation?

a. Drink at least 8 glasses of caffeinated beverages per day**
   i. Patient should drink at least 8 glasses of non-caffeinated beverages per day
b. Limit the amount of spicy food, dairy and fiber consumed
   i. Spicy food, dairy and foods high in fiber can worsen diarrhea
c. Take loperamide as needed – 4mg initially, followed by 2mg after each loose stool, up to 16 mg/day
d. Keep a log of the number of times of diarrhea per day, weight loss, food and beverages consumed