# Targeting NSCLC:
## Update On a New Therapy

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Despite being the most preventable of all human cancers, lung cancer continues to be diagnosed at alarmingly higher rates every year. It is estimated that 21,100 Canadians will have been diagnosed with lung cancer in 2003.[1] In the same year, 18,800 Canadians will succumb to the disease, making it the leading cause of cancer death for both genders.

Non-small cell lung cancer (NSCLC) is the most common form of lung cancer. It consists of the following histological types:

- adenocarcinoma,
- squamous cell carcinoma,
- large cell carcinoma, and
- adenosquamous carcinoma.

Surgical resection is considered the primary treatment for NSCLC. Unfortunately, only about 20% of cases are suitable for surgical resection upon presentation; a large percentage of these patients will eventually develop progressive disease with metastatic spread. Among the increasing number of people being diagnosed with lung cancer, about 75% will be candidates for some form of chemotherapy during the course of their disease.

### Robert's case

Robert, 63, is a new patient to your practice. He has a stage IV adenocarcinoma of the lung, with metastases to the liver. He has been followed by a medical oncologist for the last 10 months. He recently noted a slight deterioration in his shortness of breath and an increase in fatigue. He is still able to do most of his usual daily activities.

At present, he only requires salbutamol and, occasionally, acetaminophen. He has received two different forms of chemotherapy, but has had no treatment in the past three months. He will be seeing his medical oncologist soon, at which time they will discuss a new pill form of chemotherapy.

A physical examination reveals dullness to percussion at left lung base, with decreased breath sounds over that same area.

**What is Robert's prognosis and treatment?**

**What is the new form of chemotherapy he mentioned?**

**For more on Robert, see page 132.**

## What is the prognosis and treatment of advanced NSCLC?

Stage IV NSCLC, with a median survival of nine months, is incurable.[2] Therefore, the primary goal of treatment shifts to palliation. Chemotherapy is the mainstay of treatment for advanced NSCLC. Many studies have assessed the role of chemotherapy, and have concluded that it can improve disease-related symptoms when compared to the best supportive care alone. However, chemotherapy

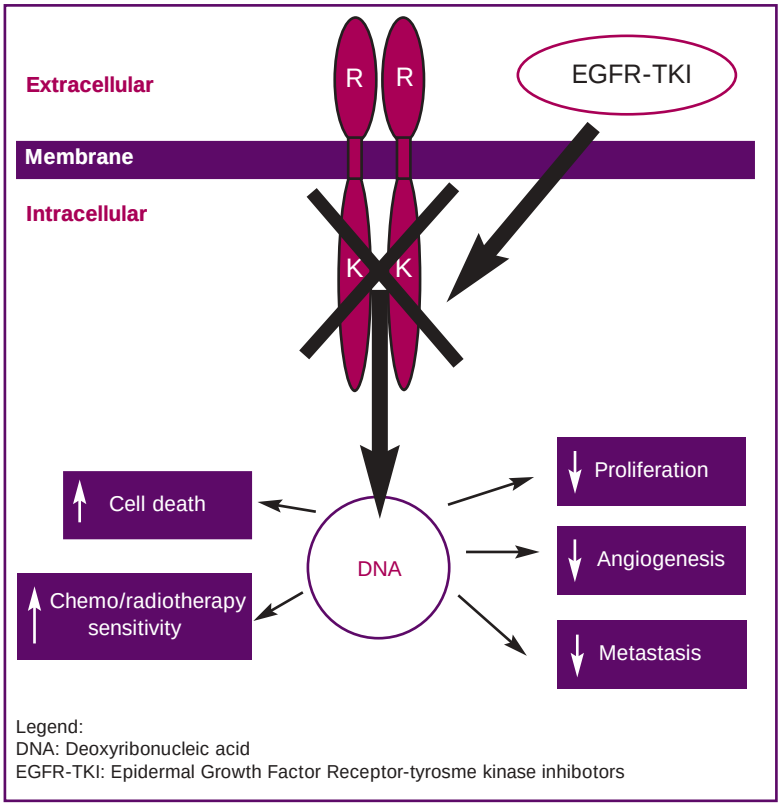


Figure 1. EGFR and inhibition of the signal transduction pathway. The tyrosine kinase enzyme located in the inracellular domain of the receptor is blocked by the EGFR tyrosine kinase inhibitor, which may result in a decrease of cell proliferation, angiogenesis, and development of metastases, while increasing cell death and sensitivity to chemotherapy and radiotherapy.

## Back to Robert's case

Robert returns to your office four weeks later. He has a new rash and would like your advice on how to deal with it. He tells you that he started on gefitinib two weeks ago. The rash has been present for about six days. Otherwise he is feeling well. He admits to an improvement in his shortness of breath, especially over the last week.

The only new pertinent finding on physical examination is a maculopapular eruption on the face, scalp and upper torso, which is associated with several pustules on the face and back.

What are the side-effects of gefitinib?

How are those side-effects managed?

produces only modest improvements, and the median survival is six to eight weeks.

Currently, platinum-based (cisplatin or carboplatin) regimens are considered standard first-line therapy in patients with advanced NSCLC. Commonly used NSCLC treatment regimens include a platinum agent combined with vinorelbine, gemcitabine, or paclitaxel. A recent study comparing four of the commonly used combinations revealed that all had similar response and survival rates.[3]

Recently, two randomized clinical studies (RTCs) assessing single-agent docetaxel reported significant improvement in quality of life and overall survival.[4,5] Docetaxel has since been approved for use in Canada, as second-line therapy for advanced NSCLC. Although better tolerated than most first-line regimens, docetaxel still has significant side-effects, including alopecia, peripheral neuropathy, and myelosuppression. Fortunately, there are newer, less-toxic agents on the horizon. A recent RTC, which compared second-line docetaxel to pemetrexed, found equivalent response rates and similar overall survival rates, but significantly less toxicities, especially with respect to neutropenias and neutropenic fevers.[6] Research on these cytotoxic agents, as well as newer targeted therapies, is ongoing.

## What is the new form of chemotherapy?

Traditionally, chemotherapeutic agents have worked by targeting rapidly dividing cells. Unfortunately, it is this same process that has led to many of the toxicities of these drugs, including mucositis, diarrhea, and myelosuppression. When the goal is palliation, these side-effects can counter the benefits gained from treatment. Much of the recent research has focused on how to be more precise in targeting the cancer.

Over the last few years, by examining the development and progression of cancer, researchers have gained a better understanding of processes, such as signal transduction, angiogenesis, and apoptosis. Many of the molecules and steps involved in these processes have been isolated, and novel agents are being developed based on these known "targets", such as the epidermal growth factor receptor (EGFR) inhibitors. "Targeted therapies" are currently being researched quite extensively for the treatment of many cancers, including lung cancer.

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## What can be said about EGFRs?

EGFRs have been identified as initiators of the signal transduction pathway and, thus, as key drivers in the process of cell growth (Figure 1). A variety of solid tumours, including NSCLC, have increased activity at the EGFR.[7] This heightened signaling within a cancer cell may, in turn, result in the promotion of tumor cell growth, blocking apoptosis, increasing production of angiogenic factors, and even facilitating the processes of metastasis. Therefore, inhibiting the EGFR would be a rational target for the treatment of NSCLC.

A new class of agents, called EGFR tyrosine kinase inhibitors (EGFR-TKIs), has been developed to target the EGFR molecules. Two oral drugs in this class have had the most success in the treatment of NSCLC: gefitinib and erlotinib. Both drugs have similar toxicity profiles and have shown single-agent activity against advanced chemorefractory NSCLC in clinical trials. In a pair of phase II studies of gefitinib,[8,9] significant antitumor responses, rapid improvement of NSCLC-related symptoms (median time of eight to 10 days), and improvement in quality of life were seen.[10] Similar promising outcomes have been seen in phase II studies of erlotinib.[11]

In December 2003, Health Canada's Therapeutic Product Directorate granted conditional approval of gefitinib (250 mg orally per day) as monotherapy for the treat-

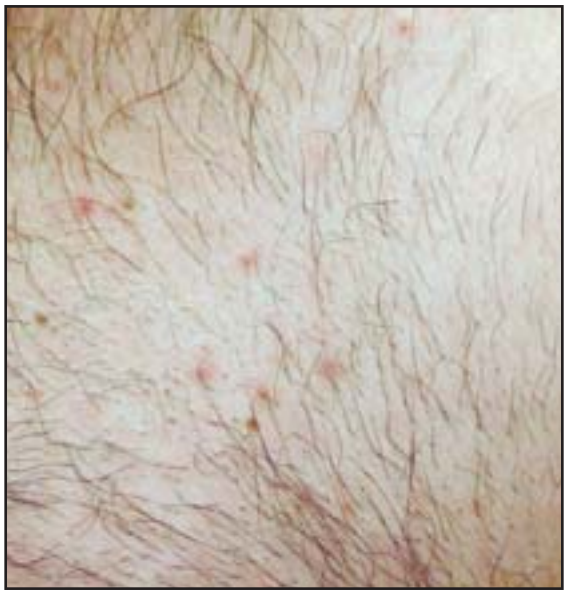

Figure 2. Acneiform rashes are a commone side-effect caused by EGFR-TKI agents. (Reprinted with permission from the American Society of Clinical Oncology[16])

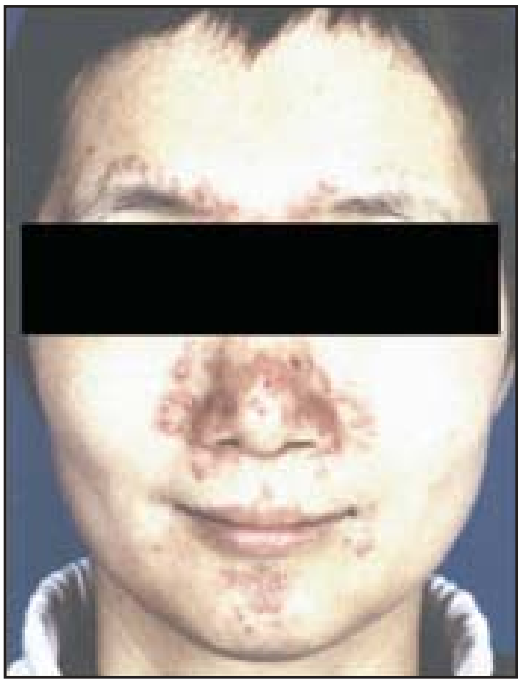

Figure 3. Grade 2 acneiform rash. (Reprinted with permission from the American Society of Clinical Oncology[16])

**Table 1**
**Treatment options**

| Skin toxicities | Treatment |
|---|---|
| Dry skin | • Good moisturizing skin lotion, without any perfumes |
| Acne | • Topical clindamycin gel<br>• Systemic minocycline<br>• Topical tretinoin<br>• Oral corticosteroids (for more intense flare-ups) |
| Pruritus | • Hydroxyzine |
| Eye irritations | • Steroid eyedrops |

ment of locally advanced or metastatic NSCLC. This treatment is applicable to patients who have failed both prior platinum-based and docetaxel chemotherapy treatments.

## What are the side-effects of EGFR-TKIs?

Gefitinib and erlotinib are generally well tolerated. Also the convenience of oral chemotherapy is highly appreciated by many patients. The most frequent side-effects are diarrhea, nausea, vomiting, and skin effects (including dry skin, rash, and acne).[12] Transient elevations in liver enzymes (transaminases) can occur, but are rarely of any clinical significance. Allergic reactions have been documented, but these are uncommon. Although the development of acute interstitial lung disease is rare, it can be life-threatening.

### Gastrointestinal toxicities

Although commonly reported, the gastrointestinal toxicities of the EGFR-TKIs are usually mild and resolve after a few days. Diarrhea is one of the most frequently noted side-effects; this can be

managed quite easily by drinking plenty of fluids, avoiding a high-fibre diet, and taking medications, such as loperamide. Nausea and vomiting are treated with antiemetics, such as prochlorperazine and dimenhydrinate. If gastrointestinal problems do not resolve, patients should contact their medical oncologist for further instructions.

## *Dermatologic toxicities*

Although the etiology of dermatologic side-effects of EGFR-TKIs has not been clearly established, it is thought to be related to the expression of EGFR in the epidermis and hair follicles.[13] All EGFR-TKI agents evaluated in clinical trials thus far have been associated with a variety of effects on the skin ranging from dryness to acneiform rashes (Figures 2, 3).

The rash typically consists of macular and maculopapular lesions. It occurs most often on the face, but may also appear on the trunk, arms, and legs. Many patients will also experience pustules at some point during their treatment. On occasion, patients may develop moderate eye irritation, including blepharitis, ingrown lashes, and mild ocular surface irritation.

Skin toxicities are usually seen within one to two weeks of starting the new therapy.[13] Even without drug-dose alteration, dermatologic symptoms tend to improve without any intervention. Should the drug be discontinued, the skin effects often will completely resolve. However, a rash alone does not necessitate discontinuation of the therapy.

Although no specific treatment has been identified as effective in all patients with skin toxicities, there are a variety of treatments which may provide some relief (Table 1).

It is important to appropriately manage patient expectations in dermatologic toxicities.[13] Patients should be informed to expect some form of skin reaction and know that this is not an allergic reaction. If patients are more prone to acne, they will be likely to experience more severe rashes. Such individuals should also avoid overexposure to sunlight, heat, and humidity, as their skin will be more sensitive to these elements. Finally, patients must understand that skin effects are usually mild to moderate and are rarely cause for concern.

## *Interstitial pulmonary fibrosis*

Cases of interstitial lung disease have been reported in patients receiving gefitinib,[14] at an overall incidence of less than 1% (33% of the cases have been fatal).

Patients present with an acute onset of dyspnea, sometimes associated with a cough or low-grade fever. These symptoms tend to be rapidly progressive, resulting in hospitalization. Patients were found to have evidence of interstitial pneumonia, pneumonitis, and alveolitis. Although indi-

**Table 2**
**Drugs which may interact with gefitinib**

- Phenytoin
- Rifampin
- Carbamazepine
- Barbiturates
- Itraconazole, ketoconazole
- Cimetidine, ranitidine
- Metoprolol
- Warfarin
- St. John's wort

viduals with a previous diagnosis of idiopathic pulmonary fibrosis have been observed to experience worsening of their condition while on gefitinib, patients without this condition or any other risk factors (such as previous thoracic radiation) have also experienced this toxicity. There is some debate as to whether this is truly an effect of the drug, or rather a progression of lung cancer. Any patient who has acute worsening of pulmonary symptoms should hold off on taking the drug until the appropriate investigations are completed.[15] If the diagnosis of interstitial lung disease is confirmed, gefitinib should be discontinued indefinitely and the patient should be treated appropriately.

## *Drug interactions*

A list of drugs which may interact with gefitinib is presented in Table 2. Many of these interactions are due to CYP3A4 metabolism.[14] Plasma levels of gefitinib have been shown to decrease when given potent CYP3A4 inducers, such as rifampin and phenytoin. Higher plasma levels are seen when combined with CYP3A4 inhibitors, such as ketoconazole. Metoprolol levels have been shown to increase by 30% when co-administered with gefitinib.[15] Any drug that lowers the gastric pH (*e.g.* ranitidine) may decrease plasma concentrations of gefitinib. There is also a risk of increasing the international normalized ratio (INR) in patients being treated with warfarin.[15] It is recommended to monitor the INR more regularly in such patients, particularly when first starting therapy with gefitinib. CME

## Take-home message

1. Advanced NSCLC is often be treated with chemotherapy, with the primary goal being improvement of disease-related symptoms and quality of life. Platinum-based regimens are standard first-line treatment; docetaxel is standard second-line treatment.
2. A new class of drugs, called epidermal growth factor receptor tyrosine kinase Inhibitors (EGFR-TKI), has been shown to improve symptoms and quality of life of patients in the third-line setting.
3. Gefitinib, an EGFR-TKI, is the first of these agents approved for use in Canada.
4. Gefitinib, though usually well-tolerated, may have some side-effects, such as diarrhea, nausea and vomiting, skin changes, and interstitial lung fibrosis. These are usually mild, and easily treated without necessitating discontinuation of gefitinib, except for the interstitial lung fibrosis.
5. There are several potential drug-drug interactions with gefitinib. If there is any concern about starting a new medication in a patient already on gefitinib, the physician should contact the pharmacist who dispensed the gefitinib.

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## Net Readings:

1. National Cancer Institute
   *www.cancer.gov/cancerinfo/pdq/adulttreatment*
2. Cancer Care Ontario: Lung Cancer Disease Site Group: Program in Evidence-Based Care
   *www.cancercare.on.ca/access_1100.htm*

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