

# Systemic Therapy of Lung Cancer

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- Systemic indicates a medication that goes throughout the body, attempting to kill tumor cells or stop tumor cell growth wherever the medication encounters them.
- Usual methods of systemic therapy include chemotherapy, small molecule inhibitors, and angiogenesis inhibitors.
- Systemic therapy of some other cancers may include hormonal therapy, such as in breast and prostate cancer, and immune modulators, such as in kidney cancer and melanoma.
- Monoclonal antibodies directed against tumor cells are widely used in the treatment of lymphoma, certain forms of breast cancer, and in some patients with colon cancer. They are just being evaluated in the treatment of lung cancer (for example, cetuximab or Erbitux®).

# Uses of Chemotherapy in Lung Cancer

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Adjuvant—given for several months following surgery or radiation therapy in an effort to kill microscopic tumor cells that may be present in the body, and prevent them from growing to become full-blown metastases. Goal of adjuvant chemotherapy is to prevent recurrence of cancer.

1. Adjuvant chemotherapy is often used in patients with non-small cell lung cancer after surgery, and involves several “cycles” of platinum-based therapy. Drug regimens may include cisplatin/vinorelbine or carboplatin/paclitaxel.
2. Recent studies indicate that such chemotherapy may increase the 5-year survival rate by as much as 10-12% in certain patient groups.

# Uses of Chemotherapy in Lung Cancer

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Neoadjuvant—given for a few weeks or months prior to local therapy of surgery or radiation. The “neo” indicates that it is the first form of therapy given to the patient.

1. This approach is sometimes used in patients with locally-advanced non-small cell lung cancer, such as with stage III disease, to get systemic therapy into the patient early to deal with microscopic tumor spread to other organs, as well as in an effort to shrink the tumor in the chest and allow it to be removed more effectively.
2. Neoadjuvant chemotherapy plus radiation therapy is also commonly used in patients with stage III disease, with the same goals as above.

# Uses of Chemotherapy in Lung Cancer

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*Treatment of Advanced Disease*—given in hopes of shrinking tumor, inducing a period of remission, and prolonging survival.

1. In stage III (locally-advanced) disease, chemotherapy before or during radiation therapy has been shown to improve the remission rate and duration, and survival prospects for patients compared with those with radiation therapy alone.
2. In stage IV (spread to other parts of the body) disease, chemotherapy has been shown to improve symptoms, induce partial remissions, and prolong survival in patients who are sufficiently fit to receive chemotherapy.

# Uses of Chemotherapy in Lung Cancer

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## Treatment of Advanced Disease —(cont'd)

3. In non-small cell lung cancer, chemotherapy commonly consists of a platinum drug (either cisplatin or carboplatin) plus a second drug (either paclitaxel [Taxol®], docetaxel [Taxotere®], gemcitabine [Gemzar®], or vinorelbine [Navelbine®]).
4. After first-line chemotherapy, a few drugs are also approved for second-line therapy of non-small cell lung cancer (pemetrexed [Alimta®], docetaxel [Taxotere®]).

# Uses of Chemotherapy in Lung Cancer

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*Small cell lung cancer*—mainstay of therapy is chemotherapy, with very high remission rates and rapid response to chemotherapy.

1. Most commonly used regimen is cisplatin/etoposide or carboplatin/etoposide.
2. Some interest recently in cisplatin/irinotecan as an alternative regimen.
3. Radiation therapy to the chest is routinely used in patient with limited-stage disease, i.e., tumor confined to the chest.
4. Radiation therapy to the brain is commonly used in limited-stage patients, in an effort to prevent brain metastases.

# Targeted Molecules in Lung Cancer

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Targeted Molecules—the first approved was gefitinib [Iressa®], now largely supplanted by erlotinib [Tarceva®]. They work by inhibiting the epidermal growth factor tyrosine kinase receptor (“EGFR inhibitors”). Cetuximab (Erbix®) is a monoclonal antibody directed against EGFR, currently in trials in lung cancer.

1. Tarceva® is approved for second-line therapy of advanced non-small cell lung cancer. The response rate is low overall, but some of the patients who respond to it will do so dramatically and for long periods of time.

2. Side effects of Tarceva® are generally mild—diarrhea, acne-like rash, rare lung toxicity.

3. Patients who appear most prone to benefit from Tarceva® appear to be women, patients with adenocarcinoma (particularly bronchoalveolar type), never-smokers, and patients of Asian descent. However, patients in all categories may potentially benefit, and should be given the drug if appropriate.

# Angiogenesis Inhibitors in Lung Cancer

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1. VEGF (Vascular Endothelial Growth Factor) inhibitors affect the new blood vessel formation in tumors. Bevacizumab [Avastin®] is FDA-approved for the treatment of advanced colon cancer, and is being evaluated in a variety of other cancer settings. It was just approved for the treatment of advanced non-small cell lung cancer, in conjunction with carboplatin/paclitaxel, showing a two-month increase in average survival over chemotherapy alone.
2. Risks include bleeding and blood clot formation. Bleeding is a particularly concerning problem, especially with centrally-located tumors in the chest, because of the risk of life-threatening hemoptysis (coughing up blood).
3. Many clinical trials are underway to better assess the role of bevacizumab in patients with lung cancer.

# Side Effects and Risks of Chemotherapy

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1. Annoying—nausea and vomiting (much less common these days with current chemotherapy drugs and better anti-nausea drugs), mouth sores, fatigue, diarrhea.
2. More serious—infection risk when white blood cells are temporarily reduced; bleeding risk when platelets are temporarily reduced.
3. Life-threatening—infections can occur that can be dangerous.
4. When chemotherapy is combined with radiation therapy in stage III patients, the normal lung tissue and normal esophagus lining can be significantly irritated. This may occasionally produce major problems breathing, or major problems swallowing. The latter may lead to problems with nutrition and hydration, and patients may need supplementary intravenous fluids or even feeding tubes temporarily.

# The Future

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1. Current and future clinical trials in advanced lung cancer mainly employ chemotherapy drugs in conjunction with targeted molecule drugs. It is unlikely that studies of adding a third or fourth chemotherapy drug to a standard two-drug combination will be useful.
2. Considerable clinical research is underway at pharmaceutical companies and in major medical centers to understand the molecular “targets” in the tumor cell, and to then develop drugs to attack those targets.
3. Much progress has been made in the past 10 years, but there is still much to be done.
4. Patient participation in clinical trials is key to advancing this field.