

Highlights from the 2008 Annual Meeting of the American Society of Clinical Oncology

Lung Cancer

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Each year, an estimated 215,000 adults in the United States are diagnosed with lung cancer. It is the second most common cancer in both men and women. The two main types of lung cancer are small cell lung cancer, which makes up about 15 percent of cases, and non-small cell lung cancer (NSCLC), which accounts for about 85 percent of cases. These two types of lung cancer are diagnosed based on how the cells look under a microscope.

The term “small cell” refers to the size and shape of the cancer cells. Small cell lung cancer begins in the nerve cells or hormone-producing cells of the lung. It is usually described as either limited stage (the cancer is located on one side of the chest) or extensive stage (the cancer has spread to other areas of the chest or outside the chest). NSCLC starts in the epithelial cells that line the airways and produce mucus to lubricate and protect the lungs.

It is important for doctors to distinguish NSCLC from small cell lung cancer because the two types of cancer are usually treated in different ways. The location and size of a lung tumor, and whether it has spread to lymph nodes or more distant sites, determine the stage of lung cancer. (Lymph nodes are a linked system of small bean-shaped structures throughout the body that helps filter out and destroy bacteria and other toxic substances.) Together, the type of lung cancer (NSCLC versus small cell) and stage of the disease determine what type of treatment is needed.

Combining Chemotherapy With Other Drugs to Treat Metastatic Non-Small Cell Lung Cancer

CHEMOTHERAPY COMBINED WITH CETUXIMAB

Researchers are so encouraged by the combination of the medication cetuximab (Erbix) and chemotherapy that it may become the new standard of care for the initial treatment of NSCLC that has metastasized (spread from its original tumor site to other parts of the body).

Clinical trials have shown that the use of cetuximab can improve the effectiveness of other treatments. For instance, combining cetuximab with radiation for head and neck cancer, and with chemotherapy for metastatic colorectal cancer, has benefited patients.

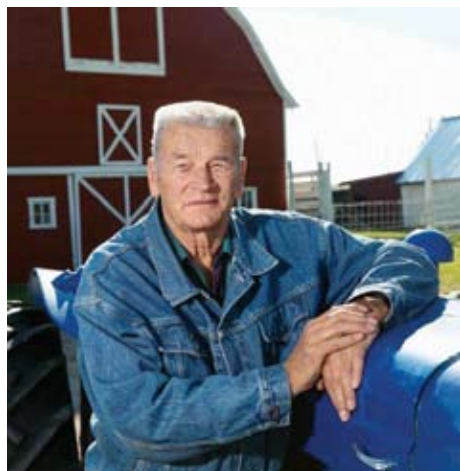
Cetuximab is a type of targeted treatment that works by blocking the epidermal growth factor receptor (EGFR), one of the key structures on the cell surface that promotes the growth of cancer cells. Unlike chemotherapy, targeted treatments attack specific molecules and cell mechanisms thought to be important for cancer cell survival and growth. This specific targeting helps to spare healthy tissues and causes less severe side effects.

Certain tumor cells contain excess amounts of EGFR. (These tumors are said to overexpress EGFR.) The more receptors present on a cell, the more signals they can transmit into the cell to stimulate its growth. Cetuximab prevents EGFR from starting this chain reaction that leads to cancer growth.

More than 1,100 people from 30 countries took part in the FLEX clinical trial. All of these participants were newly diagnosed with metastatic NSCLC. Nearly all of them had stage IV lung cancer, which means that the cancer had spread to other parts of the body. Approximately half of the people who took part in the

clinical trial received chemotherapy only; the other half of the patient group received a combination of chemotherapy and cetuximab. The chemotherapy contained two standard anti-cancer drugs: cisplatin (Platinol and others) and vinorelbine (Navelbine and others).

People who received cetuximab plus chemotherapy survived slightly longer (11 months) than those treated with chemotherapy alone (10 months). Adding cetuximab to chemotherapy also slowed the growth of the tumors and/or



caused them to shrink in more than 35 percent of the study participants, compared with less than 30 percent of those who received only chemotherapy. The benefit of cetuximab was seen in people with different subtypes of NSCLC.

Like other drugs that target EGFR, the most common side effect of cetuximab was a moderate acne-like rash that was treatable with medication.

This is reportedly the first time that a targeted treatment has increased survival when given as the initial treatment for people with all subtypes of NSCLC. These results suggest that cetuximab in combination with chemotherapy may become the new standard for first-line (initial) treatment of NSCLC. In the future, researchers may be able to pinpoint which patients with NSCLC will benefit the most.

CHEMOTHERAPY COMBINED WITH CP-751,871

Doctors are always searching for new ways to improve treatment options for people with metastatic NSCLC. Researchers from the M. D. Anderson Cancer Center in Houston, Texas, may have found one by adding a protein known as CP-751,871 to the standard chemotherapy combination of paclitaxel (Taxol and others) and carboplatin (Paraplatin and others).

CP-751,871 is a monoclonal antibody, which is a type of targeted treatment. It targets a receptor found on many tumor cells, including those of NSCLC.

One hundred and fifty people with metastatic NSCLC took part in this multicenter clinical trial. None of them had previously received treatment for their cancer. Ninety-seven patients were treated with CP-751,871 along with paclitaxel and carboplatin. The other 53 people in the clinical trial were treated with chemotherapy alone.

Among the 97 patients who received the combination treatment, the tumor shrank significantly in 52 of them (54

percent). People who had squamous cell carcinoma, a major subtype of NSCLC, did even better with the combination treatment: tumors shrank in 78 percent of these patients. Among the 53 people who received chemotherapy alone, tumors shrank in 22 of them (41 percent).

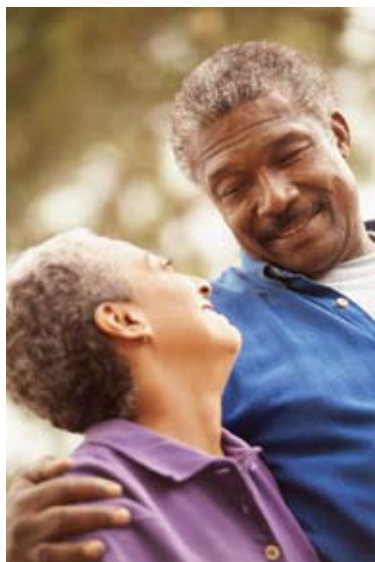
Researchers are encouraged by these early results. They plan to continue to study CP-751,871 along with paclitaxel and carboplatin in people with NSCLC, particularly those with squamous cell carcinoma.

PEMETREXED AS MAINTENANCE CHEMOTHERAPY

Chemotherapy is part of standard treatment for people with NSCLC, but until now, maintenance chemotherapy has not been a part of the standard of care. Maintenance chemotherapy is a treatment given to people three to six weeks after completing initial chemotherapy—usually with cisplatin or carboplatin—to try to prevent the cancer from growing or spreading.

However, a new clinical trial has shown that for the first time, maintenance chemotherapy with a medication called pemetrexed (Alimta) delays by 50 percent the time it takes for metastatic NSCLC to grow. (Pemetrexed is a drug approved by the U. S. Food and Drug Administration for treating NSCLC that has continued to grow despite previous chemotherapy.)

Researchers from Romania compared the use of pemetrexed maintenance therapy with supportive care (treatment of symptoms but no maintenance therapy) in more than 650 people with metastatic NSCLC. Their cancer had neither



grown nor shrunk after initial treatment with a platinum-containing medication such as cisplatin or carboplatin. Almost 450 people received pemetrexed, and about 220 received only supportive care.

The tumors of patients who received pemetrexed did not grow or spread for slightly more than four months; tumors in those who received supportive care started to grow or spread in less than three months.

The most common side effect of pemetrexed was anemia, an abnormally low level of red blood cells that can lead to extreme fatigue, shortness of breath, and other symptoms. This side effect occurred in five percent of those treated with this new medication, compared with one percent of those who were not given it.

Researchers were so encouraged by the results of this “very effective” medication, they are recommending pemetrexed be given to people with metastatic lung cancer after they complete their initial treatment with chemotherapy.

SORAFENIB FOR CHEMOTHERAPY-RESISTANT LUNG CANCER

A drug that has brought hope to people with metastatic kidney cancer may also help people with metastatic lung cancer, according to the results of a recent clinical trial.

Sorafenib (Nexavar) is a targeted treatment that was approved by the U. S. Food and Drug Administration in 2005 for metastatic kidney cancer. Clinical trials have shown that the drug shrinks kidney tumors in many people who have already tried other treatments that did not work.

Sorafenib blocks receptors for vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF)—substances that play a critical role in the growth of new blood vessels in the body and in the spread of tumors. It also slows tumor growth by interfering with the mechanisms that cancer

cells rely on to make new cancer cells.

Nearly 350 people with metastatic NSCLC took part in the clinical trial conducted by the Eastern Cooperative Oncology Group. All of these patients had already been treated with at least two chemotherapy regimens, which were not effective. In the first part of the clinical trial, they all received sorafenib by mouth twice a day for two months. People whose tumors responded to sorafenib continued with the drug. Those whose tumors kept growing and did not respond stopped their treatment.

The second part of the clinical trial focused on the 83 people whose tumors neither grew nor shrank during the first part of the study. Fifty-one people received sorafenib for two more months, and 32 people received placebo (a look-alike medication containing no active ingredient).

After two months, the tumor neither shrank nor grew in 47 percent of the people who received sorafenib, compared with only about 20 percent of those in the placebo group. Those who received sorafenib went four months without their cancer starting to grow again; those who received placebo went two months.

Researchers concluded that sorafenib is a promising option that should be studied further for people with metastatic NSCLC.

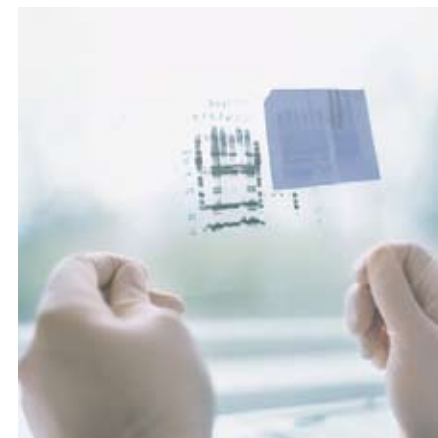
Chemotherapy After Surgery for Non-Small Cell Lung Cancer

PREDICTING THE BENEFIT OF CHEMOTHERAPY

Chemotherapy after surgery can increase survival of people with common solid tumors, including breast cancer, colorectal cancer, and NSCLC. However, about 50 percent to 65 percent of these people are treated effectively by surgery alone and do not need chemotherapy.

A new genetic test that characterizes early lung tumors by their genetic fingerprint may help doctors identify the patients with lung cancer who might benefit from chemotherapy. This test may also identify those who are not likely to benefit from chemotherapy. Such a test could spare many people with early-stage lung cancer from the side effects of unnecessary chemotherapy.

Canadian researchers analyzed tumor samples from more than 60 people who had not received chemotherapy after surgery for NSCLC. The researchers identified a set of 15 genes that distinguished people at high risk of recurrence from those at low risk of recurrence—that is, how likely it is for their cancer to come back after treatment. Some of these genes help control the growth and death of cancer cells or regulate other cancer-related genes. The patients' risk level was verified by medical records.



Next, the information on these 15 genes and their predictive power was applied to another group of people who had received chemotherapy after surgery for NSCLC. In this group, the genes identified 67 patients as being at high risk of recurrence. After following these people, researchers found that they actually did benefit from the chemotherapy they had received. On the other hand, 66 people who were identified by the gene test as being at low risk of recurrence were observed to gain no benefit from their chemotherapy.

This study was a follow-up analysis from the original National Cancer Institute of Canada's Clinical Trials Group study JBR.10. The JBR.10 trial consisted of nearly 500 participants and was

conducted in collaboration with the National Cancer Institute in the United States.

In the future, when this test has been verified, doctors may be able to spare people with low-risk cancer the side effects of unneeded chemotherapy while identifying those who could benefit from such chemotherapy. Currently, this test is only available through a clinical trial.

LONG-TERM RESULTS WITH CHEMOTHERAPY

The potential use of the genetic test discussed above becomes even more important in light of results from the International Adjuvant Lung Cancer Trial (IALT). This clinical trial showed that, for people with NSCLC who have had surgery, chemotherapy does offer a benefit. But that benefit declined over the long term.

Usually, the recommended treatment approach is to follow up surgery with chemotherapy containing the drug cisplatin. This recommendation is made on the basis of the IALT, in which more than 1,800 people took part at nearly 150 centers around the world. All of them had surgery for their cancer. Half of the group was treated with cisplatin-based chemotherapy, and the other half was not.

For the first five years after treatment, chemotherapy extended the survival of patients who received it, compared with those who did not. However, this benefit did not appear to last beyond five years. Between six and eight years after treatment, people treated with chemotherapy were less likely to survive than those who did not receive chemotherapy.

Researchers are continuing to study the possible reasons for this declining benefit to chemotherapy after five years. As with any cancer treatment, they encourage people to talk to their doctors about the best treatment for their individual situation.

Small Cell Lung Cancer

RADIATION TO PREVENT LUNG CANCER FROM SPREADING TO THE BRAIN

To reduce the chance of small cell lung cancer metastasizing (spreading) to the brain, doctors use preventive radiation to the brain, also called prophylactic cranial irradiation (PCI). Researchers conducted a clinical trial testing two different doses of PCI to see which would more effectively prevent metastases to the brain.

More than 700 people with limited-stage small cell lung cancer took part in this clinical trial at 157 centers in 22 countries. At the start of the clinical trial, none of the people had any sign of cancer in their brain; all had already received chemotherapy.

The participants were divided evenly into two groups. One group was treated with PCI at the standard dose of 25 Gy (Gy being a unit measure of radiation), given in 10 parts (or “fractions”) once a day over 12 days. People in the second group were treated with PCI at a higher dose of 36 Gy, which was given in the standard 18 once-daily fractions spread out over 24 days or on an accelerated schedule of 24 fractions given twice a day for 16 days.

Two years after treatment, cancer had spread to the brain in 30 percent of patients treated with the standard PCI dose, compared with only 24 percent of those treated with the higher dose. However, more people treated with the standard dose survived than did those who received the higher dose (42 percent versus 37 percent).



Researchers concluded that PCI at 25 Gy should remain the standard of care for treating people with limited-stage small cell lung cancer. This important study, experts say, should help guide the use of radiation for these patients.

TOPOTECAN PLUS CISPLATIN FOR EXTENSIVE-STAGE SMALL CELL LUNG CANCER

The standard first-line treatment for people with extensive-stage small cell lung cancer is the combination of cisplatin and etoposide (VePesid and others). Another combination has been studied in a clinical trial to see how it compares with this established approach.



Researchers from 84 centers in Germany and Austria were pleased to discover that cisplatin plus topotecan (Hycamtin) may be just as beneficial as the standard treatment. Topotecan is an anti-cancer drug used to treat certain gynecologic cancers. The clinical trial results suggest that cisplatin plus

topotecan may be a worthwhile alternative treatment for people with extensive-stage small cell lung cancer.

Nearly 700 people took part in the clinical trial. These people had never before received chemotherapy. About half of the patients were treated with the combination of topotecan and cisplatin. The others received the standard combination of cisplatin and etoposide.

All of the patients survived between 9½ and 10½ months regardless of the treatment they received. However, those who received cisplatin plus topotecan went one month longer without their cancer growing than those who received the

standard cisplatin/etoposide treatment (about seven months versus about six months).

The new combination of topotecan and cisplatin also seemed to more effectively shrink the cancer. Tumors shrank significantly in 56 percent of the patients who received the newer combination, compared with 46 percent of those who received the standard combination. The tumor completely disappeared in approximately 10 percent of those in the topotecan/cisplatin group, compared with about seven percent of those in the cisplatin/etoposide group.

Based on the results of this clinical trial, researchers say that the combination of topotecan and cisplatin is certainly as good as the combination of cisplatin and etoposide in helping people with this type of lung cancer survive. And, they added, the newer combination may be even better at shrinking tumors in these patients.

Please note: Although the treatments discussed in this chapter are showing promise, most are still in clinical trials—some in earlier phases of research—and may not be available yet to the general public. Your doctor can help guide you as to which new medications could be right for you and whether you are eligible to take part in the clinical trials of these new treatments.