A Breath of Fresh Air: Lung Cancer Survival Shows Some Improvement

Although lung cancer is still the most common non-skin cancer for both men and women in the United States and remains a difficult cancer to treat, there has been an incremental improvement in survival — especially 1 year out from diagnosis. This improvement is thought to be largely due to improved surgery and surgical techniques, although for small-cell lung cancers — a highly aggressive form of lung cancer comprising 25% to 30% of all cases — chemotherapy has played the most significant role.

Overall, however, lung cancer survival is "still pretty grim," concedes Bruce Johnson, M.D., former head of the Lung Cancer Biology Section at the National Cancer Institute, even though "it has gotten a bit better." Median survival for lung cancer has gone up by several months in the past several years, while 5-year survival has doubled for small-cell lung carcinomas, said Johnson, now at the Dana-Farber Cancer Institute in Boston.

According to data from NCI’s Surveillance, Epidemiology and End Results Program (SEER), 5-year survival rates for lung cancer rose from 12.1% in 1975 to 13.9% in 1990; this includes both categories of lung cancer — small-cell lung cancer and non-small-cell lung cancer, which accounts for the other 75% to 80% of all cases. When measured in 1-year intervals, lung cancer survival for both has increased from 34.2% to 40.5% over those same years.

"Fifteen years ago, the 1-year survival rates for metastatic lung cancer were around 15%, and now survival approaches 30% to 35% . . . so there is improvement," said Ramesh Ramanathan, M.D., a clinical researcher at the University of Pittsburgh Cancer Institute. (Approximately 70% of small-cell lung cancers have metastasized at the time of diagnosis, according to Ramanathan, who did not have similar data for non-small-cell lung cancer.) He contends that improved surgical techniques may have played a role in incremental increases in survival.

"Surgery is of paramount importance in non-small-cell carcinoma and that is where almost all the cures come from," said Johnson. Five-year survival for this type of cancer is 15% to 17% — three times that for small-cell lung cancer.

Michael Kelley, M.D., an NCI investigator, attributes incremental lung cancer survival to improved surgical techniques, as well as to declining morbidity and mortality related to surgical resection, and to the development of potent antibiotic support.

Although non-small-cell lung carcinoma responds fairly well to surgical intervention, small-cell lung cancers are much more responsive to chemotherapy and radiation. "For small-cell lung carcinoma, chemotherapy has impacted survival in a big way. In terms of absolute prolongation of survival, it has increased [survival] four- or five-fold," said Kelley. Nevertheless, there has only been "a modest survival advantage from systemic chemotherapy for non-small-cell lung cancer, which makes up the bulk of lung cancer cases."

Johnson, who while at NCI supervised chemotherapy trials for patients diagnosed with lung cancer, attributes progress in survival for small-cell lung carcinoma to the ability to give combined modality treatment — radiation combined with chemotherapy — relatively effectively without inflicting a lot of side effects. Because only 1% to 3% of this patient population are potential candidates for surgical resection due to the metastasis and aggressive growth of small-cell lung cancer, it becomes pertinent to find other treatment modalities.

Johnson said that "one of the big problems is second cancers" for people who survive lung cancer initially (see Review, Sept. 16, 1998, p. 1335). Currently, there are large ongoing trials to determine if secondary tumors can be prevented using chemopreventive agents.
“Chemical Genetics” Speeds Up Drug Discovery

Behind electronically locked lab doors, drug companies spend upwards of 10 years and $300 million dollars to bring a typical new drug to market. From afar, the process looks controlled and rational. But more than 90% of new drugs are found by throwing enormous numbers of molecules at a target protein, then looking for a lucky match. It’s a matter of numbers over elegance.

“The fact that we’re still doing this [drug development] randomly is an admission of temporary defeat,” said Timothy Mitchison, Ph.D., a cell biologist at Harvard University, speaking to science journalists at a November conference in Boston. Confusion about how small molecules like drugs interact with huge proteins like enzymes and cell receptors is hindering more directed drug design, said Mitchison, who added that finding new drugs is slow and uncertain. Although Mitchison foresees random screening to be the status quo for the next decade, some drugs have already been built from scratch to fit target proteins. Mitchison cited HIV protease inhibitors as the most spectacular of these.

Meanwhile, though drug discovery is largely scattershot, a powerful automated tool called combinatorial chemistry has sped up the process immensely. The process works by quickly synthesizing thousands of similar molecules, then testing them for drug action with target proteins.

Finding molecules — which are potential drugs — the right size and shape to dock with these proteins traditionally has been akin to picking through dozens of hardware bins to find just the right gear. In contrast, with the automated methods of combinatorial chemistry, researchers can quickly scan the whole hardware store. Finding a hit or near miss yields a template molecule that can be used to chum out hundreds of similar potential drugs.

An Academic Move

Over the past 5 years combinatorial chemistry has swept through the pharmaceutical industry. But the process is expensive, so it remains tucked inside drug company fortresses.

Four new NCI-funded academic centers are looking to change that by advancing this fast-forward drug screening and moving it into the public domain (see sidebar). By researching tools and technologies instead of searching for specific drugs, the centers will also catalog the functions of proteins, a tricky, but essential, component of drug development, especially for cancer.

One of the new centers, Harvard’s Institute of Chemistry and Cell Biology, is co-directed by Mitchison, who said that only one out of every 1,000 human proteins is now a drug target. Many more of the estimated 200,000 proteins could be targeted for disease therapy,