lites of the carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK).

“The reduction was just not as great as you would have expected based on how much [the study participants] had cut back,” said lead researcher Stephen Hecht, PhD.

Hecht and colleagues enrolled more than 150 people who smoked, on average, 23.7 cigarettes a day. The study involved gradual cigarette reduction using nicotine replacement therapy and brief counseling sessions. At each stage of the program, urinary levels of the NNK metabolites 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and NNAL glucuronides (NNAL-Gluc) were measured. The reductions in these biomarkers did not keep pace with the reductions in cigarettes.

Cutting cigarette consumption by 53% led to a reduction of only 29% in NNAL and NNAL-Gluc. Cutting cigarettes by 75% caused only a 37% drop in the chemicals. Even people who cut back to just 2.6 cigarettes a day, a reduction of 90%, lowered their levels of NNAL and NNAL-Gluc by only 46%.

Although these reductions in carcinogens were statistically significant, for most smokers the effect was modest and transient, Hecht said. As the study went on, NNAL and NNAL-Gluc increased again in many participants, even though they were still smoking fewer cigarettes. Compensatory smoking is probably the reason.

Thun and Hecht said their findings support the notion that giving up cigarettes entirely is the best bet for reducing the health risks caused by tobacco. In the first study, quitting reduced lung cancer risk substantially; people who gave up smoking before age 35 had almost the same lung cancer risk as nonsmokers, but even those who quit after age 55 saw a substantial reduction. Hecht has done previous research showing that levels of NNAL and NNAL-Gluc gradually decrease and eventually become undetectable in people who quit smoking.

Moreover, no product or strategy designed to reduce the harm from smoking has yet been shown to work, Hecht said.

“I still think cessation is the way to go, clearly,” he said. “We don’t have conclusive evidence that anything else works.”

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VACCINE TRIALS SHOW ACTIVITY IN KIDNEY AND LUNG CANCER

The recent successes of two therapeutic cancer vaccine trials have focused attention on the recent progress and future potential of harnessing the immune system’s power to fight cancer.

In a study published in the Journal of the National Cancer Institute (2004;96:326–331), researchers from Baylor University Medical Center at Dallas and colleagues reported results of a Phase I/II multicenter trial involving 33 patients with Stage II or IV nonsmall cell lung cancer. The vaccine caused complete responses in three patients lasting six months, 18 months, and 22 months. In seven other patients, the disease did not progress for a period ranging from five months to 28 months, while an eighth patient experienced a 30% reduction in the size of the lung nodule.

The vaccine, called GVAX (Cell Genesys, Inc., San Francisco, CA), was made from autologous tumor cells genetically modified to secrete human granulocyte-macrophage colony-stimulating factor, a protein that stimulates the lymphocytes to attack the cancer cells.

Lead researcher John Nemunaitis, MD, said this was the first time immune therapy alone has been shown to be effective against metastatic nonsmall cell lung cancer. Nemunaitis, Director of the Mary Crowley Medical Research Center at Baylor and Director of the US Oncology Phase I research program, called the results promising for patients with this disease, which is frequently resistant to chemotherapy.
The second study, published in *The Lancet* (2004;363:594–599), described results from a Phase III trial of a vaccine designed to prevent progression of organ-confined renal cell carcinoma after nephrectomy. Vaccine production included an in vitro incubation with interferon γ to increase its immunogenicity. Dieter Jocham, MD, and colleagues report that the autologous renal tumor cell vaccine improved progression-free survival at five years from 67.8% in the control group (no adjuvant treatment) to 77.4% in the vaccine group. At 70 months, the figures were 59.3% for the control group compared with 72% in the vaccine group. Jocham, a Professor of Urology at the University of Lübeck Medical School in Germany, and colleagues concluded, “According to our results, application of an autologous renal tumor cell vaccine can be considered in patients undergoing radical nephrectomy due to organ-confined renal-cell carcinoma of more than 2.5 cm in diameter.”

These and similar trials are “suggestive of something that’s potentially very important,” said Jeffrey Schlom, PhD, Chief of the National Cancer Institute’s Laboratory of Tumor Immunology and Biology. “The field is progressing exponentially in terms of knowledge and the types of vaccines that are being used,” he said. “This is a very exciting time.”

In the lung cancer vaccine trial, the most common side effect was relatively mild (Grade 1 or 2) irritation at the injection site. Only 12 vaccine-related adverse events were noted in the renal carcinoma vaccine trial, and these were of mild to moderate severity. So far there have been extremely few toxic side effects in vaccines that have been tested, Schlom said.

Researchers are pursuing numerous avenues in the search for more effective cancer vaccines. In both of these vaccines the autologous cells are modified by adding immunostimulatory substances like cytokines, either during an in vitro incubation or by adding an activated cytokine gene. Other researchers have used dendritic cells to make an antigen more immunogenic, or have modified poxviruses or adenoviruses to express tumor antigens.

“Some of these vaccines are just entering into clinical trials, some have been in trials for a few years, but it takes years to find out if they work,” Schlom explained.

Progress is slow for a number of reasons, not least of which is the complexity and delicacy of the immune system.

Schlom sees another major obstacle to vaccine therapy: the nature of the clinical trials process itself.

Phase I trials generally test a new therapy in patients who have failed to respond to all conventional treatments. But this type of trial is a poor setting for testing a cancer vaccine, Schlom said. Because many conventional cancer treatments are cytotoxic therapies, the immune systems of patients in these trials may be too damaged to respond effectively to the vaccine. Moreover, patients in this situation typically have a very large tumor burden. Not only does a large tumor depress the immune system, it makes any immune response less likely to succeed.

“When you give a vaccine you can induce just so many T-cells in the body, and then it’s hand-to-hand combat with the tumor cells,” Schlom explained. Killing 100 tumor cells is far easier than killing 1 billion.

Testing vaccines in combination with other conventional cancer therapies also poses challenges if a cytotoxic drug doesn’t “play well” with the vaccine because it inhibits the immune system, Schlom said.

Despite the inherent difficulties involved in the research, Schlom is optimistic about the progress that is being made. “The field is moving very rapidly in a very science-based way—there are parallel programs going on, several of which look very good.”

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