“Cigarette use among adolescents has been going down without adding young people to another product. While it is entirely speculative whether e-cigarettes are having any impact on cigarette use among youth, it is not speculative that the widespread use of nicotine products by youth is harmful.”

In the Aug. 5, 2014, Wall Street Journal, Siegel wrote, “The gateway hypothesis is a myth. Of the few nonsmoking youths who do experiment with e-cigarettes, there is currently no evidence that they subsequently progress to cigarette smoking.”

Siegel also cites a study by Theodore Wagener, Ph.D., assistant professor of general and community pediatrics at the University of Oklahoma Health Sciences Center in Oklahoma City. In a survey of 1,300 college students, average age 19 years, about tobacco and nicotine use, 43 students said their first nicotine product was an e-cigarette, and of that group, only one person claimed to go on to smoke regular cigarettes.

However, Wagener’s numbers are minuscule compared with those in a study that Glantz co-wrote, which found that e-cigarettes act as a gateway to nicotine addiction. Appearing in the July 2014 issue of JAMA Pediatrics, this study was based on answers from 17,353 U.S. middle and high school students in 2011 and 22,529 in 2012 who took part in the National Youth Tobacco Survey both years.

“The emerging data is showing rapid market penetration of e-cigarettes among never cigarette smokers, particularly low-risk kids. While about 10%–20% of kids using e-cigarettes have never smoked a cigarette (we believe) there is high dual use among kids. It is highly likely that many of these kids started with e-cigarettes and added cigarettes later.”

Denise B. Kandel, Ph.D., professor of Sociomedical Sciences in Psychiatry at Columbia University In New York, and Eric R. Kandel, M.D., professor and director at Kavli Institute for Brain Science at Columbia University, and senior investigator, Howard Hughes Medical Institute, Chevy Chase, Maryland who proposed the gateway theory of drug addiction years ago, said the main concern shouldn’t be whether e-cigarettes are better for the respiratory system, but rather how nicotine affects the developing brain. In the Kandels’ latest study (N. Engl. J. Med. 2014;371:932–43; doi:10.1056/NEJMa1405092) Denise Kandel wrote, “Nicotine acts as a gateway drug on the brain, and this effect is likely to occur whether the exposure is from smoking tobacco, passive tobacco smoke, or e-cigarettes.”

Denise Kandel said she’s concerned that “the behavior is outpacing the science, and this is a serious problem. There is a tremendous increase in the use of these cigarettes, and there’s very little research carried out to address the basic questions that we need answers for. Could it possibly undo 50 years of public-health work to reduce nicotine addiction? I think so.”

Myers echoes a similar sentiment and adds that it is imperative that the U.S. Food and Drug Administration speed up enactment of its proposed set of rules issued last April.

“This is truly using America’s youth as guinea pigs in one of the largest experiments ever conducted, with no rules,” he said. “While we debate whether the large numbers of youth who are using e-cigarettes will go on to using cigarettes, basic public health principles say we should be doing everything possible to prohibit marketing and sale of these products to kids.”

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Checkpoint Blockade Immunotherapy for Cancer Comes of Age
By Vicki Brower

Cancer immunotherapy—Science’s 2013 breakthrough of the year—took off in 2014. Almost weekly, reports described patients on immunotherapies living longer than those taking combinations of chemotherapy and targeted drugs.

One immunotherapy has reenergized the field. Ipilimumab (Yervoy), the first checkpoint inhibitor developed, approved in the U.S. in 2011, is the culmination of more than two decades of research. Ipilimumab is an antibody that inhibits cytotoxic T lymphocyte-associated protein 4 (CTLA-4), an immune checkpoint receptor found on T cells. CTLA-4 normally acts as a brake on the immune system’s ability to unleash T-cell attack on cancer cells. But ipilimumab releases the brake, allowing T cells to attack cancer.

About 20% of patients with advanced melanoma who take the drug live 3 years or longer, whereas previously median survival was 7–8 months. However, ipilimumab works well only in one-fifth of patients. Scientists recently discovered the reason and, for the first time with any immunotherapy, could predict who will benefit. Jedd D. Wolchok, M.D., Ph.D., chief of the melanoma and immunotherapeutics service at Memorial Sloan-Kettering Cancer Center in New York, and team analyzed tumor samples from 64 patients treated with ipilimumab or a similar drug, tremelimumab (N. Engl. J. Med. 2014;371:2189–99; doi:10.1056/NEJMoa1406498). The researchers discovered an association in many, but not all, patients, between mutational load and clinical benefit.

“We then asked, What did the immune system ‘see’ to evoke a reaction in responders?” Wolchok said. A genetic signature in these patients caused tumors to express new antigens (neoepitopes) that T cells recognize and become more reactive to. The researchers then validated the signature in a second set of 39 melanoma patients treated with anti–CTLA-4 antibodies. The reactive antigens are similar to many viral and bacterial antigens to which the body normally reacts as well.

“These data suggest that the neoepitopes in patients with strong clinical benefit from CTLA-4 blockade may resemble epitopes from pathogens that T cells are likely to recognize,” Wolchok said.

“This is the first reliable way to predict which patients with melanoma will respond to ipilimumab, which will help guide upcoming trials and therapy design,” said coauthor Timothy A. Chan, M.D., Ph.D., vice chair of the radiation oncology department and director of the
translational oncology division. The team is applying these techniques to study responses to other immunotherapies in trials, including PD-1 (programmed death protein 1) checkpoint blockers in melanoma and other cancers.

“We are hoping to refine this into a test which will help inform medical decision making in the future, but this is a work in progress,” Wolchok said. He is considering several options to treat nonresponders, including combinations of immunotherapies, oncolytic viral therapies, targeted pathway inhibitors, and chemotherapy or radiation, he said.

“Early results with checkpoint inhibitors offer both proofs of concept and some dramatic clinical results,” said Richard D. Klausner, M.D., chief medical officer and senior vice president of Illumina in San Diego. Many previous efforts to activate the immune system to fight cancer were less successful than recent trials with checkpoint blockers.

“This is because it was thought that just turning on the T-cell receptor should be sufficient to produce a response,” said Padmanee Sharma, M.D., Ph.D., of the department of genitourinary medical oncology at the University of Texas M. D. Anderson Cancer Center in Houston. “That did not pan out,” she said.

But the discovery of CTLA-4 in the 1990s by James Allison, Ph.D., then at the University of California, Berkeley, now at M. D. Anderson, led to experiments to block this off-signal to increase antitumor immune responses and ultimately tumor rejection. That breakthrough led to ipilimumab and laid the basis for research on another T-cell–inhibitory pathway, PD-1. But broad patents on the CTLA-4 pathway, compared with those on the PD-1 and PD-L1 molecules, have limited efforts to develop other CTLA-4 inhibitors, Sharma said.

Immunotherapy has several advantages over other treatments. Unlike chemotherapy and targeted therapies, immunotherapy is well suited to cancers with many mutations and may need to be given only once or a few times. Roy S. Herbst, M.D., Ph.D., chief of medical oncology and professor of medicine and pharmacology at Yale University, noted that the pluses of immunotherapies include “their specificity, memory or durability, and adaptability.” Still unresolved are questions including the best endpoints for trials and how best to deal with adverse effects (such as gastrointestinal and lung) and cytokine release syndrome, which can cause many complications and differ from side effects of other therapies.

Until recently, most efforts focused on melanoma and renal cell cancer, long known to be immunogenic. But with new genetic research, such as Wolchok’s, that focus is changing. Most trials combine CTLA-4 inhibitors with several other treatments. F. Stephen Hodi Jr., M.D., director of the Center for Immuno-Oncology at Boston’s Dana-Farber Cancer Institute, recently led such a study. Patients with metastatic melanoma treated with ipilimumab survived significantly longer, a median of 17.5 months versus 12.7 months, if they simultaneously received granulocyte–macrophage colony-stimulating factor (GM-CSF), which stimulates growth of white blood cells (JAMA 2014;312:1744–53; doi:10.1001/jama.2014.13943). In the 245-patient phase II study, 68.9% of those taking the combination survived for 1 year, compared with 52.9% of those taking ipilimumab only.

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Hodi said that he and his team had reason to believe that this combination would be beneficial from synergies seen in preclinical studies between CTLA-4 blockade and GM-CSF–secreting tumor vaccines. Improved antigen presentation with GM-CSF by recruiting macrophages and dendritic cells may account for the synergy. Early clinical research also shows that this combination could benefit patients with prostate and ovarian cancers.

This trial showed two intriguing results beyond survival benefit. First, although overall survival differed, both arms had the same median progression-free survival, 3.1 months. One reason may be that some immunotherapies produce necrotic and/or inflammatory tissue around tumors, which may appear as tumor growth on a scan, Hodi said. “This effect was also seen with sipuleucel-T, or Provenge, in prostate cancer [an autologous cellular immunotherapy],” he added. Second, more patients on monotherapy reported serious side effects, 44.9%, than those on combination treatment, 53.3%. Two patients taking the combination died, from cardiac arrest and a perforated colon, whereas seven taking ipilimumab alone died, from colon, multiorgan, respiratory, and liver failure. The combination regimen’s improved adverse-effect profile contributed to overall survival rates, the authors observed. As for why the combination was superior, they noted that GM-CSF protected gastrointestinal mucosa from severe colitis in preclinical and clinical studies. Fewer toxic effects to the lung also occurred with the combination, which the authors attributed to GM-CSF’s lung-protectant qualities.

In another combination study, Yale researchers tested ipilimumab with the PD-1 immune checkpoint inhibitor nivolumab in a phase I/II trial initially with 53 patients with advanced melanoma, with an update given at the 2014 American Society of Clinical Oncology (ASCO) meeting in a total of 94 patients (N. Engl. J. Med. 2014;369:122–33; doi:10.1056/NEJMoa1302369). The updated trial yielded a 1-year overall survival rate of 82% and a 2-year overall survival of 75%. Patients responded similarly regardless of BRAF mutation status, and as of June 2014 the median duration of response had not been reached (ASCO 2014 abstract LBA9003).

“It makes sense to combine them, as each had demonstrated considerable activity in this indication as monotherapies,” said lead author Mario Sznol, M.D., Yale professor of medical oncology. Of the original 53 patients in the trial, with more time, complete response rate increased from 10% to 17%. Sznol said that figure was probably an underestimate, since 22 (41.5%) of those patients experienced tumor reduction of more than 80%, with many experiencing near-complete responses. However, toxic effects with the combination increased, with 62% having grade 3/4 side effects, which were manageable and reversible. Twenty-two
Breast Irradiation Therapy Innovations Forgo Permanent Marks, Minimize Treatment

By Anna Azvolinsky

Many women who had radiotherapy for breast cancer bear small, dark ink dots on their chest—a permanent reminder of diagnosis and treatment. Radiation oncologists use these to mark the area to irradiate.

But many patients are reluctant to receive these permanent body markings, which can be visible in bathing suits and other clothing. Steven Landeg, M.Sc., senior radiographer, and colleagues at the Royal Marsden Hospital in London found a solution: tattoos visible only under ultraviolet (UV) lighting. The UV light excites the dye, making it fluoresce.

At the National Cancer Research Institute Cancer Conference 2014, the researchers presented their 46-patient randomized study comparing traditional black tattoos with the new invisible one (http://conference.ncri.org.uk/abstracts/2014/abstracts/8291.html). Both types yield equally accurate delivery of radiotherapy. Although the fluorescent dye had been used to mark the site of a tumor biopsy before surgery to reduce risk of error, this is the first time the dye was used in breast cancer radiotherapy.

Applying fluorescent tattoos to guide radiotherapy modestly increased average pretreatment time, from 19 minutes, 3 seconds to 21 minutes, 4 seconds (P = 0.37; not statistically significant). Likewise, treatment time increased modestly, from 10 minutes, 5 seconds to 11 minutes, 4 seconds (P = 0.06; not statistically significant).

“I am glad my tattoos will only be visible under special lights and I will be able to complete my radiotherapy with no lasting signs,” one anonymous patient wrote.

Fifty-six percent of patients receiving the fluorescent tattoo had improved body image satisfaction 1 month after treatment, compared with 14% who received a dark-ink tattoo. A worse body image satisfaction at 1 month occurred in 22% and 50% of patients who received fluorescent and conventional tattoos, respectively. The researchers will soon submit full efficacy data and their approach for publication. Now they work to implement the new technique in routine practice, because the data are sufficient evidence that the fluorescent ink does not compromise consistent delivery of radiation, Landeg said.

“This is a cost effective alternative that is likely to improve the experience of breast radiotherapy for a proportion of this large population of women so we endeavor to implement invisible tattoos into routine clinical practice in early 2015,” he said.

“A lot of women complain about the [permanent] tattoos. Having something that is invisible except under a certain type of light is great,” said Michael D. Alvarado, M.D., associate professor of surgery at the University of California, San Francisco. (He was not involved in the study.) Alvarado said he would still like to see data on how long the fluorescent tattoos last to ensure the marks are still there at least 5 years after application in case retreatment or treatment of the other breast is necessary.

Reshma Jagsi, M.D., D.Phil., associate professor of radiation oncology at the University of Michigan Health System in Ann Arbor, who also was not involved in the study, agreed.

“This is an important pilot study. We need to do everything possible to minimize the long-term impact of breast cancer treatment on our patients as many patients go on to long-term survivorship.”

patients stopped treatment because of toxic effects, and one patient died from colitis-related multiorgan failure.

Scientists at ASCO’s 2014 meeting discussed preliminary results of a phase I trial in metastatic renal cell cancer with the same combination at two doses. The objective response rate was 29% with a higher dose of nivolumab and 39% for a higher dose of ipilimumab; duration of response was 4.1–22.1 weeks and 6.1–18.3 weeks, respectively. An expansion trial at these doses and at a third, equal high dose is ongoing. A phase III trial comparing the combination with each drug alone is under way.

Researchers are now seeing checkpoint blocker activity outside melanoma and renal cell carcinoma, Herbst said. Lung cancer, once thought nonimmunogenic, is also the subject of several ipilimumab trials. A phase II study combining ipilimumab with paclitaxel and carboplatin showed a median overall survival of 12.2 months for phased ipilimumab, 9.7 months for concurrent ipilimumab, and 8.3 months for control in untreated patients. Those results serve as the basis for an ongoing phase III trial in non–small-cell lung cancer (NSCLC) and SCLC. It is also in phase II testing with chemotherapy before surgery for NSCLC and in a phase I trial with the targeted drugs erlotinib or crizotinib for patients with stage IV NSCLC who also have mutations in the gene for epidermal growth factor receptor or anaplastic lymphoma kinase. A phase I trial of ipilimumab plus imatinib (Gleevec), a c-Kit inhibitor, is ongoing for patients with advanced cancers, including lung cancer.

Ovarian cancer and other trials are also under way, including a phase II study with ipilimumab and a phase I with tremelimumab and MEDI4736, an anti–PD-L1 immunotherapy in advanced solid tumors, including colorectal cancers. Combination nivolumab and ipilimumab is in a phase II clinical trial for recurrent glioblastoma. Ipilimumab is also in two phase I trials in adults with Hodgkin lymphoma and a phase II trial in mesothelioma.

“Despite many, many unanswered questions, I think that it is safe to say that we have finally, after decades of research, begun to open an important new chapter in the treatment of cancer via the manipulation of the immune system,” Klausner said. “That said, we are still in the early days of the therapeutic potential of immunotherapy—and the rules, the generalizability, and the persistence of therapeutic benefit are all questions whose answers are ahead of us,” he added.

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