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 drug 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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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 fluorescent.

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.”
Not all institutions chose the permanent ink route, however, such as the University of Texas M. D. Anderson Cancer Center in Houston. Benjamin Smith, M.D., associate professor of radiation oncology, and colleagues drew the radiation field with nonpermanent markers and use Tegaderm, a sticky, clear plastic bandage, to protect the marks. Drawing many nonpermanent dots on patients allows radiation oncologists to delineate the whole treatment field instead of having just a few radiation exposure borders, Smith said.

If fluorescent tattoos are widely implemented, patients must be custodians of their own treatment care plans, Jagsi said. Should a patient require radiation treatment years later, she will need to disclose that she had radiation and that fluorescent tattoos were applied so that new treatments can account for prior treatments.

According to Beryl McCormick, M.D., F.A.C.R., chief of external-beam radiotherapy at New York’s Memorial Sloan–Kettering Cancer Center, fluorescent tattoos would benefit darker-skinned patients, on whom black-ink tattoos are harder to see. “These newer tattoos would resolve this problem and also save women from having permanent reminders of their treatment,” she said.

Partial- Versus Whole-Breast Irradiation
Researchers also work to reduce radiation therapy for breast cancer while maintaining good long-term outcomes. One way is to minimize exposure of healthy tissue to radiation by administering partial-breast irradiation (PBI) to only the tumor bed rather than whole-breast radiation (WBI).

“PBI has been going on for a long time, despite limited level 1 evidence of smaller randomized studies to support its utilization initially,” Alvarado said.

This is why breast cancer clinicians await results from the large National Surgical Adjuvant Breast and Bowel Project (NSABP) B-39 study (https://clinicaltrials.gov/ct2/show/NCT00103181), comparing PBI and WBI which should yield results in the next 18 months-2 years. The trial is recruiting 3,000 stage 0, I, or II patients to receive either WBI or one of three modes of PBI.

“I think this study will really, in a major way, define the indications for PBI,” Smith said.

The American Society for Radiation Oncology gives conservative guidance, which Smith helped write, for when offering PBI to patients may be appropriate. A committee is updating this consensus statement, published in 2009 Smith said.

“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.”

Shorter Radiation Courses May Be Better
Meanwhile, the UK Standardization of Breast Radiotherapy (START) A and B trials (Lancet Oncol. 2013;14:1086–94) enrolled more than 4,400 women. Ten-year follow-up data show that 3–4 weeks of more intensive radiotherapy works as well as the standard therapy course of 5–7 weeks. Although the per-treatment dose is higher with the shorter course, the total delivered dose over several weeks is lower. Women who received 40 Gy delivered in 15 fractions over 5 weeks or 39 Gy in 13 fractions had local or regional recurrence rates similar to those of women getting the standard 50-Gy dose in 25 fractions.

“Coupled with other trials of WBI, [these results] are sufficient to justify changing practice,” Smith said.

Moreover, the shorter course costs less, causes less burden, and is at least as tolerable, for appropriately selected patients, Jagsi said.

Quality-of-life data from both patients and their clinicians, collected in a smaller, randomized, M. D. Anderson study comparing standard with shorter WBI, suggest that patients who received the shorter radiation course had less fatigue and could better care for their families.

“I didn’t expect this result,” Smith said. “The dogma for a long time was that if you increase the dose per treatment, then there would be more long-term side effects. But what the START-B and [M. D. Anderson] data show is that the shorter course is probably better for patients.”

Women in these studies represent typical breast cancer patients in either the U.S. or the UK: older than 50 years, with early-stage estrogen receptor–positive disease, and for whom American Society for Radiation Oncology guidelines recommend shorter therapy.

But although the shorter treatment has been adopted by some medical centers and physicians in the U.S., the majority have yet to make the change, Smith noted.

Confirming this assertion, authors of a new study analyzed commercial insurance data from more than 15,000 women who had lumpectomies followed by WBI (JAMA 2014;312:2542–50). Use of shorter-duration WBI increased between 2008 and 2013. However, among women older than 50 years and for whom shorter radiotherapy is recommended, use was only 10.6% in 2008 and 34.5% in 2013.

“For many decades, we have been taught that giving radiation in bigger per-day doses can be dangerous for patients in the longer term and result in worse cosmetic results,” Jagsi said. “So there has been some reluctance in the radiation oncology community to rush to embrace an approach with bigger daily radiation doses until people are really assured that it is safe. But now that we have evidence, uptake is increasing.” (See Int. J. Radiat. Oncol. Biol. Phys. 2014;90:1010–6 and 2014;90:1001–9.)

Another trial still under way, RTOG 1005, addresses whether an even more accelerated course of WBI—3 weeks, with a concurrent radiation boost to the tumor bed—works as well as standard WBI.

Jagsi said now that longer-term data from several studies are available, it’s clinicians’ responsibility to “get on the bandwagon and make sure shorter radiotherapy is offered to appropriate patients. I think this is one of the most important things we can do—promoting uptake of less expensive, more convenient approaches to radiation therapy for our patients whenever possible.”

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