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Going Off-Label

Physicians are legally permitted to prescribe drugs approved for one purpose to be used for another, a practice called off-label prescribing. The rise of targeted therapies and immunotherapies is creating new challenges for navigating off-label options.

by **Kate Yandell**

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WHEN TORI TOMALIA'S *oncologist gave her a new prescription for pills to treat her stage IV non–small cell lung cancer (NSCLC) in November 2013, she expected it would be filled routinely. Instead, the pharmacist told the 37-year-old that her insurance company had declined to cover the prescription and that she would need prior authorization for the medication.*

Her new therapy, Xalkori (crizotinib), had been approved by the U.S. Food and Drug Administration (FDA) in 2011 to treat advanced NSCLC patients with ALK gene mutations in their tumors. Tomalia, a mother of three and the owner of a brewery and theater in Ann Arbor, Michigan, instead had learned her cancer had a mutation in the gene ROS1. Clinical trial data had indicated that patients like Tomalia whose cancers had the ROS1 mutation did well on Xalkori, so her oncologist prescribed it. This practice, called off-label treatment, is legal and common in medicine.

Tomalia's insurer ended up covering her Xalkori prescription off-label for more than two years. In March 2016, the drug was approved by the FDA to treat ROS1-positive metastatic NSCLC patients. Tomalia is still taking Xalkori to keep her tumors at bay, except for brain metastases, which are being treated separately. Meanwhile, oncologists are now prescribing Xalkori off-label to a new group of NSCLC patients whose tumors have alterations in the MET gene based on promising clinical trial results.

The rise of immunotherapies and targeted agents is complicating off-label treatment, making it more attractive, but also providing opportunities for patients to try drugs that have not been well-tested in their type of cancer. And while using a new therapy off-label before it has been fully investigated can extend life for some patients, off-label use can come with financial and logistical hurdles.

A Cancer Treatment Staple

Off-label use of drugs can be cutting-edge or routine. Studies suggest that historically, from 30 to 50 percent of prescriptions in oncology in the U.S. have been off-label. Off-label uses that become standard-of-care treatments are listed in treatment guidelines, such as those compiled by the National Comprehensive Cancer Network (NCCN). Patients might not even know that the drug they are using is not technically approved by the FDA for their cancer type.

When Larry Simpson of Mobile, Alabama, was first diagnosed with stage IV head and neck cancer in 2014 at age 70, he was given radiation and chemotherapy with carboplatin and Taxol (paclitaxel). Both drugs had been originally approved for treating ovarian cancer: carboplatin in 1989 and Taxol in 1992. Today, Taxol is approved for several additional cancer types, and the NCCN guidelines support off-label use of carboplatin, Taxol or both to treat more than a dozen cancer types, including head and neck cancer like Simpson's.

In January 2015, Simpson completed chemotherapy and radiation treatment, but by the summer, a positron emission tomography (PET) scan revealed that his cancer was growing aggressively. He consulted with a local doctor, who suggested he travel to the University of Texas M.D. Anderson Cancer Center in Houston, more than 450 miles from his home.

At M.D. Anderson, Simpson was enrolled in IMPACT2, an initiative in which patients get their tumors sequenced and are funneled into clinical trials based on the results. Simpson learned his cancer had a mutation in the gene PIK3CA, and he was enrolled in a trial testing a combination of Torisel (temsirolimus), which targets a pathway of which PIK3CA is a part, and Avastin (bevacizumab), which slows growth of blood vessels that feed tumors. Torisel is approved for kidney cancer. Avastin is approved, alone or in combination with other drugs, for some patients with colorectal, lung, brain, kidney, cervical and ovarian cancers. Neither drug has been approved for head and neck cancer, and the NCCN does not include these therapies in its guidelines for head and neck cancer treatment.

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Exploring Trials

Clinical trials are testing off-label use in patient with advanced cancers who have exhausted standard treatments.

A Dose of Caution

Some patients, like Simpson, receive approved drugs as part of clinical trials testing whether the drug could be useful for patients beyond the group identified in the drug's FDA label. In other cases, patients may be prescribed drugs off-label by their physician outside the context of a clinical trial. Despite some encouraging outcomes, physicians and scientists urge caution in choosing off-label treatments outside of a trial that are not considered standard and are not listed in the NCCN guidelines. "As physicians, we are in a tough spot," says Jonas de Souza, a medical oncologist specializing in head and neck cancer at the University of Chicago Medicine. "We want to treat our patients, provide them the best care available. With all the advances in oncology, there is the potential to start prescribing things we don't have evidence for yet."

Immunotherapy drugs, which unleash the body's immune system to treat cancer, are attractive for off-label use, both because they achieve notable results in some people and because for many, the side effects are easier to control than those of chemotherapy. "There's a high potential of [saying], 'Oh, let's try Keytruda in this cancer' before the evidence is there," de Souza says.

In a poster presented in March 2017 at the American Society of Clinical Oncology (ASCO) Quality Care Symposium in Orlando, Florida, de Souza and his colleagues assessed data from insurance claims for off-label use of Keytruda, which is approved for treating advanced NSCLC, melanoma, classical Hodgkin lymphoma and squamous head and neck cancer. Looking at data from private insurance and Medicare and Medicaid claims

from January 2015 to September 2016, the researchers found that 292 out of 871 patients who put in claims for Keytruda were taking the drug off-label.

Anecdotal evidence that someone with a certain condition has benefited from a drug is not sufficient to conclude it will help other people with that condition, says George Demetri, a medical oncologist specializing in sarcoma at the Dana-Farber Cancer Institute in Boston. He recently published a case study on a patient with leiomyosarcoma who was treated with Keytruda and had a very positive response. But other patients with the same disease treated with Keytruda did not benefit. Even in cancers for which immunotherapy drugs have been approved, not all patients respond to treatment, Demetri says.

In the realm of targeted therapy, researchers are learning that drugs targeting specific mutations only sometimes work across different cancer types. Mekinist (trametinib) and Tafinlar (dabrafenib), for example, are approved to treat melanoma with mutations in the BRAF gene. Data from a phase II trial have indicated that the combination is effective in BRAF-mutated NSCLC, and oncologists are adopting the treatment off-label, says Nathan Pennell, a thoracic oncologist at Cleveland Clinic in Ohio. However, BRAF-targeting drugs do not appear to work in colon cancer patients, Pennell says.

Ross Camidge, a thoracic oncologist at the University of Colorado Cancer Center, adds that cancer patients should be especially cautious about taking drug combinations outside of a clinical trial that have never been tested together in humans. “You have no idea if these drugs are going to interact,” he says. Two drugs that, taken separately, have manageable side effects could have dangerous ones in combination.

Camidge also stresses that patients should see if an off-label treatment is being tested in a clinical trial. If it is feasible for patients to join such a trial, they should do that. Their data could help establish whether the drug will be effective for other patients.

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Assessing Therapies

Know what tips to follow when considering off-label drug use with your physician.

Payment Pushback

Off-label use of drugs can raise financial and logistical concerns for patients. By law, Medicare is required to cover any off-label treatment that is supported by one of five compendia. These reference guides, published by private organizations such as the NCCN, recommend therapies based on clinical evidence. Private insurers determine which drugs they will cover off-label on a case-by-case basis, but they usually do cover treatments that are considered standard.

Patients whose claims for off-label drugs are denied can go through the appeals process with their insurance company. This may include providing evidence of the drug’s effectiveness in the form of research papers or conference presentations. At the same time, patients may want to apply for financial assistance from the drug manufacturer. Each drug company handles financial assistance differently, but patients may need to supply information on their finances and income.

The Targeted Agent and Profiling Utilization Registry (TAPUR) study, sponsored by ASCO, is taking another approach, hoping to help patients access appropriate off-label cancer drugs while testing whether they work. “The drugs are expensive, they’re not standard of care and insurance is generally unwilling to pay for them,” says Richard Schilsky, chief medical officer of ASCO. If patients do manage to get off-label treatments, there is no mechanism to collect data on whether the treatments help, Schilsky says. “TAPUR was really set up to try to solve those problems.”

So far as part of TAPUR, seven drug companies have donated supplies of 17 therapies for treatment of patients with advanced cancer who have undergone tumor sequencing. (Although TAPUR supplies the drugs at no cost, patients must supply results from their own tumor sequences, which can incur costs.)

In Simpson’s case, Medicare paid for his use of Torisel and Avastin, but only after he and his wife, Cherry, went through considerable stress wondering if they would be responsible for the expense. Some trials provide FDA-approved drugs being tested for a purpose outside their label at no cost to patients, but this is not always true. In the case of the IMPACT2 study, Simpson was asked to sign paperwork stating that he or his insurance provider would be responsible for the cost of the study drug. Determined to start the trial, he signed the papers. “We just took a leap of faith,” says Cherry. Simpson ended up taking Avastin and Torisel through the IMPACT2 trial for five months. He suffered side effects, including painful anal fissures, and his cancer progressed. In March 2016, the couple left Houston, where Simpson was being treated, and headed home.

Back in Alabama, Simpson and his wife searched for local clinical trials. They found one for the immunotherapy drug Opdivo (nivolumab), which at the time was approved only for treating melanoma and lung cancer. But the trial was in Birmingham, Alabama, 250 miles from Mobile, and the couple worried about the distance and expense. So Simpson’s local oncologist decided to prescribe Opdivo off-label. Medicare denied Simpson’s claim for coverage, but he got financial assistance through the drug’s maker, Bristol-Myers Squibb. Simpson started the drug in July 2016, and after it was approved for head and neck cancer in November 2016, Medicare did cover it.

Simpson is so far doing well on Opdivo. The couple has gone on three cruises, taking some of their six grandchildren with them each time. They are also taking the opportunity to make thoughtful end-of-life plans for both of them. “We’re living life and enjoying it and at the same time we’re getting our affairs in order,” Cherry says.

Kate Yandell is a writer and editor and was formerly the digital editor of *Cancer Today.*

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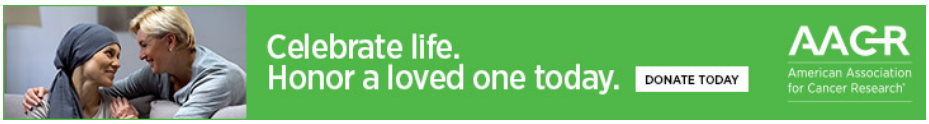
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