The Side Effect Roulette of Cancer Treatment

Researchers and advocates strive to offer patients a more accurate window into a drug's impact on daily life.

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The stomach pain stopped Vickie-Lee Wall in her tracks. "The first time the pain got that bad, I honestly thought something had burst in my gut," said the 64-year-old New Jersey woman, who has stage 4 lobular breast cancer.

Her oncologist had prescribed two drugs, including a targeted medication called abemaciclib [Verzenio], after the cancer spread to Wall's spine in 2018. Initially the pain was relatively mild. But then it ratcheted up until, three months later, Wall begged her physician for relief. "The next visit with him I went, 'I can't do this at this dose.'"

Wall, who usually checks the label before starting a new medication, notes that abdominal pain is listed as a possible side effect of the drug. But while a few others, such as diarrhea, were described as potentially severe, there was no such wording regarding abdominal pain, she said.

People with cancer typically assume that side effects from chemotherapy and other drug treatments are part of the tradeoff to treat a life-threatening disease. But some researchers and patient advocates maintain that the information provided about potential side effects, particularly more subjective ones like pain and fatigue, doesn't necessarily provide the real-world insights that cancer patients crave.

Clinical trials typically are well designed to measure the effectiveness and safety of cancer drugs, but they often don't similarly capture "the tolerability side" that patients really care about, said Hillary Andrews, director of regulatory and research partnerships for the Friends of Cancer Research, a nonprofit advocacy organization based in Washington, D.C. "They want to understand how others have experienced this drug, and how it could potentially impact them," she said.

For instance, a patient's diarrhea may not be frequent enough to constitute a safety concern but still be urgent enough that someone is reluctant to leave home, Andrews said. Federal officials have begun to encourage drug study leaders over the last decade to collect more such information related to tolerability, called patient-reported outcomes. But it's not required, and neither is the reporting of those patient measures, including on the drug label, she said.

Proponents acknowledge that adding more questions to cancer drug studies should be pursued carefully, ensuring that the findings are relevant to patients and that data collection doesn't become overly burdensome. The bottom line, though, is that getting a better handle on a drug's tolerability matters because it influences whether the patient will stick with the treatment, said Devin Peipert, a researcher at Northwestern University's Feinberg School of Medicine in Chicago who studies patient-reported measures.

Patients drop out of drug studies for various reasons, including the progression of their cancer. But "sometimes it's because the patient or the doctor has felt that the patient just has reached a level of side effects that is not tolerable," he said. "And within that, it's the patient just saying, 'I'm not going to do this anymore.'"

In drug studies, researchers track hundreds of potential side effects and other adverse events — from nausea and anemia to hospitalizations and deaths — using a set of criteria such as those established by the National Cancer Institute. Some side effects and drug toxicities are identified through blood work and other lab testing. Others involve self-reported symptoms, such as fatigue or diarrhea.

Clinicians collect that information from patients and, in the U.S., typically grade the side effects' severity on a five-point scale based on the federal agency's criteria, with 5 referring to an adverse effect that results in death. Side effects that aren't considered life-threatening are typically graded from 1 to 3; grade 3 abdominal pain, for example, describes pain that's severe enough to limit basic self-care, such as bathing or dressing oneself. Wall, when she learned about that grading criteria, wrote in an email to Undark: "I'd say doubling over is definitely a 3 on their scale."

But the collected details usually "are not patient-reported outcomes that are directly from the patient — these are interpretations of clinicians," said Michelle Tregear, chief programs officer at the National Breast Cancer Coalition, a D.C.-based research and lobbying organization.

Clinicians often underreport the frequency and severity of symptoms compared with what patients share, research has found. One 2015 study, which looked at three randomized trials involving 1,090 patients, found that physicians consistently underreported six side effects, including constipation, hair loss, and nausea. For example, half of patients across the three studies reported constipation, but physicians only reported it for 18.6 percent of patients.

Moreover, these clinician-collected reports about side effects are further distilled in research papers, said Bishal Gyawali, an oncologist at Queen's University in Ontario who is concerned about what he describes as "minimizing language" in cancer research. His research has found that the summaries of such side effects can downplay the severity of what's detailed in tables and other sections of the full study.

In a 2018 analysis, Gyawali and colleagues looked at 122 cancer drug studies published in five major medical journals. Nearly half of them, 43%, included wording in the abstract, conclusion, or discussion section that seemingly minimized the adverse effects when compared with the data itself. (Gyawali said he focused on those sections because they are most frequently read by busy

clinicians.) The words, which he described as vague and subjective, included “acceptable,” “manageable,” “feasible” or “tolerable,” among other terminology.

Based on his analysis, such language was sometimes used even though the clinicians had reported the side effects as grade 3 or grade 4 on the National Cancer Institute’s five-point scale, Gyawali said. For diarrhea to be rated as grade 3, he noted, a patient must report more than six bowel movements each day — above and beyond their typical bathroom habits. “Then having that diarrhea for two weeks, three weeks, five weeks — that’s obviously not well-tolerated despite whatever people may claim,” he said.

These words get under Tregear’s skin when she sees them in study publications. “Manageable. Tolerable. Adverse events. To who? And are you really getting that from the patient?”

A patient’s tolerance of side effects may vary depending upon their age, how advanced the cancer is, and other circumstances, Tregear said. Patients with early-stage breast cancer may be more willing to accept the treatment’s toxic effects, she said. “They can see an end in sight — the hope is that with these treatments you’re curing it.” As cancer advances, the patient’s focus may be more on quality of life. But, she added, patients should be given better insights into the experience of other patients to better make those treatment decisions.

Bridgette O’Brien was diagnosed in 2019 with stage 4 colon cancer. Since then, she has gone through a battery of treatment, including four surgeries, radiation, and more than 100 rounds of chemotherapy. The 39-year-old Minnesota woman, who leads global marketing strategy for a manufacturing supplier along with raising two young boys, is now on her sixth type of chemotherapy.

Through various drug treatments she’s suffered stretches of intense nausea and fatigue, neuropathy, weight gain, nose bleeds, dry mouth, and a pause in her periods, which turned out to be permanent. When O’Brien is prescribed a new drug, she’ll ask her clinical team about potential side effects, look at the manufacturer’s website, and search on social media forums to check out what other patients report.

Still, “the side effects have never scared me away from wanting to do whatever I think is going to help me survive,” she said. “I’m of the mindset, ‘Give me all that you’ve got.’”

Patients themselves may be reluctant to discuss the extent of their side effects, rather than risk stopping the treatment, said Donald Sullivan, a lung cancer physician and researcher at Oregon Health & Science University, who has written about physician-patient communication. “I’ve always been impressed by what some patients will tolerate, and just not tell me that they are not doing well.” For a more candid take, Sullivan will often ask the patient’s spouse or other family member how their loved one is faring.

In conversations with cancer physicians, Wall has noticed that they tend to “gloss over” potential side effects. But she sympathizes with their dilemma. “Because, quite honestly, if they sat there and they went through every possible side effect with you, who would take the drugs?”

Wall, a systems engineer consultant who reluctantly retired after the rigors of cancer surgery and other treatment, has weathered various side effects and discomforts since she was diagnosed nearly 10 years ago. But the gut-punching pain she was experiencing wasn't tolerable, she said, recalling several attacks before she sought her oncologist's help. "They were becoming progressively more painful," she said. She suspected abemaciclib was to blame, given that stomach pain was a potential side effect of the drug, and that she had only recently started taking it.

One day Wall was out shopping when the pain flared again and she doubled over, clutching the cart. "I went, 'Nope. Not doing this," she said. "Don't want to know what the next one feels like.'"

Wall's oncologist initially cut her twice-daily dose from 150 milligrams to 50. But then he got nervous, she said, that such a low dose would undercut the drug's ability to treat the cancer.

After some further dosing adjustments, the sweet spot for Wall — with continued but manageable pain — proved to be 50 mg in the morning and 100 mg at night. Wall has shared her experience, and the details of her modified dose, with others on cancer social media forums.

When asked about the potential for severe abdominal pain, Tracy Henrikson, a spokesperson for Eli Lilly and Company, abemaciclib's manufacturer, provided two studies involving the drug. In both, roughly one-third of patients reported any degree of abdominal pain; no more than 2.2 percent described it as grade 3.

Researchers and federal agencies are moving to fill the information gap. Gyawali recently co-founded an international organization called Common Sense Oncology, which includes cancer physicians, patient advocates, and others with the goal of promoting the development of more cancer drugs that notably improve patients' overall survival or quality-of-life. A wealth of data is already collected from patients in any drug study, he pointed out. Why not also ask them, he proposed, if they could tolerate the drug or not, and repeat that question at different points in the clinical trial?

Even within the tight word limits of a study abstract, those results could be shared, Gyawali said. Instead of vaguely describing the drug as well-tolerated, he suggested that researchers could write: "60% of patients thought that this drug was well-tolerated throughout the course of treatment."

And increasingly, drug studies are including some measures of the patient's experience, said Peipert, the Chicago researcher who studies patient-reported measures. The National Cancer Institute has developed such measures, which can be added to their standard set of adverse events reporting criteria. Food and Drug Administration officials also recommend the inclusion of patient-reported outcomes, including through draft guidance to the drug industry published in 2021.

But could adding these additional metrics make data collection too burdensome? It's a balancing act to collect vital patient reports while not making the process too onerous, said Joseph Unger, an

associate professor at Fred Hutchinson Cancer Center and a biostatistician and health services researcher with SWOG Cancer Research Network, a U.S.-based trials group. To ease the strain, SWOG strives to keep the time involved with reporting patient outcomes to no more than 15 to 20 minutes each time study data is collected, he said.

Patient outcomes can be collected electronically, such as through a smartphone. But study participants should also be given the option to report on paper, Unger said. He was involved with a study abstract, published this year, that found that only 9.3% of participants enrolled in a recent SWOG study chose electronic reporting.

Earlier this year, Peipert participated in an FDA workshop that discussed whether a single measurement could capture the patient's view of a drug's tolerability. Considered as a complement to specific patient-reported outcome measures, the question, he said, would be designed to assess: "What's the overall assessment of that from a patient's perspective?"

But to date, not many of these patient measures have been added to drug labels, according to a 2022 study published in Frontiers in Pharmacology. Just 8.3% of the 108 cancer drugs approved by FDA officials from 2010 until 2020 included some patient-reported outcomes on the label. The percentage was higher in Europe, with 30.2% of 139 approved drugs including at least some patient-reported symptoms.

One promising step by FDA officials, Andrews said, is a pilot initiative launched in 2020 called Project Patient Voice. The goal is to publish patient-reported symptoms that were collected during clinical trials but not reported on the drug label due to space limits and other constraints.

But the pilot's website still only lists one drug, which treats lung cancer. The FDA declined an interview request to discuss Project Patient Voice. But in an email, Lauren-Jei McCarthy, a press officer for the agency, wrote that "the FDA hopes to expand this to include more cancer drug trials." McCarthy also sent an agency response citing other efforts to encourage more collection of patient measures, including through its 2021 draft guidance.

Meanwhile, patients continue to crowdsource from others on social media, to supplement information from their clinicians and drug materials, Wall said. Cancer survivors also can offer reassurance to others, reminding them that everyone's experience with side effects may be different and not to assume the worst, she said.

"That is a major point of those forums existing to my mind," she said. "We help each other with that information. People come in and say, 'I was newly diagnosed. They want to give me this. Is anybody on it? What can you tell me about it?'"

Charlotte Huff is a Texas-based journalist who writes about the intersection of medicine, money, and ethics. Her work has appeared in KFF Health News, Nature, STAT, Texas Monthly, and The Washington Post, among other publications.

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