Beyond Chemotherapy

A new generation of precision cancer therapies are easier to tolerate than traditional treatment.

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Traditionally, cancer treatment has relied on surgery, radiation and chemotherapy—or "slash, burn and poison." While chemotherapy is often effective, it's not very discriminating. Cytotoxic chemo drugs kill fast-growing healthy cells as well as malignant ones, which can lead to a wide range of side effects. Until the late 1990s, most people with cancer could expect to receive chemotherapy as their first, and sometimes only, treatment option. But things are changing, and a growing number of patients are eligible for newer, better-tolerated therapies.

The side effects of chemotherapy—including nausea, low blood cell counts, hair loss and painful peripheral neuropathy—are well known. In fact, some cancer patients dread them so much they're reluctant to start treatment.

"I often tell people it was the chemo that nearly killed me and not the cancer," says breast cancer survivor Megan-Claire Chase. "I experienced multiple side effects that were so severe that my quality of life has been deeply impacted. I have chemo-induced peripheral neuropathy in my hands and feet. Now, I sometimes walk with a cane. As someone who used to dance and walk gracefully, this has really impacted my self-confidence. I beat cancer, yet I'm reminded of the chemo trauma every day."

Over the past two decades, targeted therapy and immunotherapy have ushered in a new era of precision medicine for cancer. These treatments home in on tumors, often with less collateral damage to normal cells.

"New advanced cancer treatments are able to more specifically treat cancer while sparing normal healthy cells, which can result in fewer side effects," says Yung Lie, PhD, president and CEO of the Damon Runyon Cancer Research Foundation. "These side effects, when severe, can result in patients discontinuing their treatment prematurely, allowing cancer cells to resume their growth."

Yung Lie, PhD, of the Damon Runyon Cancer Research FoundationCourtesy of Damon Runyon Cancer Research Foundation

Gentler treatment is a particular priority for older people, who may have more difficulty tolerating aggressive chemotherapy. “We know from prior research that older adults generally value other factors, such as quality of life and maintenance of physical function, over survival,” says Daneng Li, MD, of the City of Hope cancer center, who is studying personalized supportive care for older patients.

The need for better-tolerated treatment is also a big concern for people living with cancer long term.

“For those of us living with metastatic breast cancer, our treatment never ends until we die. It’s a

marathon, not a sprint," says patient advocate Kelly Shanahan, MD. "We need—and deserve—not only effective treatments but treatments with fewer side effects. It's one thing to tolerate nausea for four rounds of early-stage chemo and quite another to be expected to tolerate it for months upon months or even years. Quantity of life without quality is no life."

In addition to tolerability, some newer drugs are more convenient and less disruptive to daily life. Many targeted therapies are pills, while chemotherapy usually requires IV infusion. "One of the advantages of oral meds is freedom—not being tied to a chemo chair every week or every three weeks," Shanahan adds.

New Approaches

Over the years, a better understanding of how cancer develops and spreads has led to refinements in treatment.

Novel minimally invasive techniques allow surgeons to remove tumors using smaller incisions, which reduces damage to surrounding tissue and speeds recovery time. Radiation therapy has improved too, with new methods that pinpoint tumors. And for some patients, a wait-and-watch approach that defers therapy in favor of active surveillance may in some cases allow them to avoid aggressive treatment altogether.

But the biggest changes in treatment involve systemic therapies, that is, medications that affect the whole body. Based on a growing understanding of the molecular biology of cancer and how the immune system responds—or fails to respond—scientists have developed new treatments that block proteins involved in cancer cell proliferation and metastasis or spur immune cells to fight cancer.

"An understanding of the genetic changes underlying specific cancers has led to the development of targeted therapies designed to attack cancer cells that contain alterations in certain genes," Lie explains. "Other cancers respond to immunotherapy, which unleashes the body's own immune system to attack the cancer cells."

Novel therapies have changed the paradigm for two of the most common malignancies: breast cancer and lung cancer. One of the earliest targeted therapies, trastuzumab (Herceptin), approved in 1998, targets the HER2 receptor, which is highly expressed in about 20% of breast tumors. Today, there are over 100 approved targeted therapies for numerous types of cancer.

For people with non-small-cell lung cancer (NSCLC), there are now approved targeted drugs for eight so-called driver mutations that trigger uncontrolled cell growth (ALK, BRAF, EGFR, KRAS, MET, NTRK, RET and ROS1). A recent study found that 50% of tumor samples from smokers and 78% to 92% of samples from never smokers had potentially treatable mutations. The advent of these medications, along with immunotherapy, has contributed to the notable decline in lung cancer mortality in recent years. (See "Finding Grace in Adversity.")

Even for patients who still receive chemotherapy, there's a trend toward shorter treatment

duration, fewer drugs and more personalized risk assessment, rather than deploying the big guns right away for all patients. The TAILORx trial, for example, found that a majority of women with early breast cancer could safely skip chemotherapy based on a low risk score for disease progression. Antibody-drug conjugates combine the best of both worlds, using targeted monoclonal antibodies to deliver potent chemotherapy drugs directly to tumors.

What's more, efforts are underway to make chemotherapy easier to tolerate. Former Damon Runyon clinical investigator Peter Cole, MD, of Rutgers Cancer Institute of New Jersey, is working on ways to prevent chemo brain, or impaired cognition, in children with leukemia. Damon Runyon fellow Elise Jeffery, PhD, of the University of Texas Southwestern Medical Center, is investigating ways to repair bone marrow damage due to chemotherapy or radiation, while fellow Chuchu Zhang, PhD, of Harvard Medical School, is exploring the biological mechanisms underlying chemo-induced nausea.

Limitations and Barriers

Despite their promise, novel therapies have their limitations, and they're not for everyone—at least not yet.

Many people do not have tumor mutations that would make them eligible for targeted therapies. Some of the genetic alterations targeted by available drugs are rare. For example, only around 1% to 2% of NSCLC patients have ROS1 driver mutations. But the Food and Drug Administration recently approved the first drug targeting KRAS, which plays a role in around a third of all cancers. While each specific mutation may occur only in a small proportion of people, as more drivers and corresponding drugs are discovered, the better the odds that a patient will have at least one of them.

Checkpoint inhibitor immunotherapy, likewise, does not work for everyone or for all kinds of cancer. Across cancer types, fewer than half of patients respond, and it is not easy to know in advance who will benefit. These therapies work best for so-called hot, or inflamed, tumors that have many mutations and attract T cells (for example, NSCLC and melanoma), but they aren't very effective against cold tumors that lack these immune cells (for example, ovarian cancer and prostate cancer).

Faster and less expensive genetic testing has been key to the wider use of these newer therapies, enabling doctors to design customized regimens for each patient. This includes both genomic testing of tumors and genetic testing for inherited (germline) mutations, such as BRCA. In the past, oncologists tested for recognized genetic alterations one at a time, but next-generation sequencing makes it possible to search for multiple mutations in a single tumor sample or blood sample, known as a liquid biopsy. Other tests look for biomarkers (such as PD-L1), tumor mutation burden and deficient DNA repair mechanisms, all of which predict response to checkpoint inhibitors.

The use of genomic testing is expanding, and a growing number of insurers cover it, but it's still mainly done for people with recurrent or metastatic cancer.

“Without next-generation sequencing, patients with advanced cancer are doomed to take old-style chemotherapy,” says retired oncologist, breast cancer survivor and patient advocate Elaine Schattner, MD. “If you’ve got terminal cancer and want treatment, your doctor has a responsibility to look for changes in your tumor that could inform treatment, and insurers have an obligation to pay for these diagnostic tests.”

But universal testing of everyone with early-stage cancer remains controversial. Vinay Prasad, MD, MPH, of the University of California at San Francisco, cautions that widespread testing could lead doctors to prescribe drugs that target specific mutations but have not yet been shown to provide clinical benefits, such as improved survival.

What’s more, newer treatments come with their own side effects. Some targeted therapies block proteins that play a role in the growth of normal cells as well as malignant ones. Checkpoint inhibitors can lead to excessive inflammation that can harm organs throughout the body. And these treatments are often taken for longer periods than chemo.

“Everyone thinks that traditional IV cytotoxic chemotherapy is the worst when it comes to side effects, but that’s not necessarily true,” says Shanahan. “Oral targeted therapies can be just as debilitating and in some cases perhaps even worse.”

Change Takes Time

For many patients, chemotherapy remains the mainstay of treatment. Because chemo drugs work pretty much the same in everyone, they require less expertise. As new driver mutations, targeted drugs and biomarkers are continually being discovered, it can be difficult for nonspecialists to keep up. And some oncologists are hesitant to try newer therapies for which they have less evidence from randomized clinical trials and less experience with real-world use.

“Though today, an individual patient may see their treatment simply—‘My doctor found an EGFR mutation in my lung cancer, and this targeted therapy is shrinking my cancer dramatically’—the reality is that it took a decade to determine the efficacy and toxicity of EGFR inhibitors, find the appropriate dose, discover the tumor gene mutations that predict sensitivity and ultimately determine that they were better than chemotherapy as an initial treatment for appropriate patients,” says David Jackman, MD, of the Dana-Farber Cancer Institute.

David Jackman, MD, of the Dana-Farber Cancer InstituteCourtesy of Dana-Farber Cancer Institute

In addition, newer medications are more expensive than older chemotherapy drugs (many of which have generic versions), and insurers may be reluctant to cover them. In practice, access to cutting-edge therapies may depend on where someone is treated, contributing to disparities for

Black and Latino, low-income and rural patients.

Chemotherapy and newer therapies are hardly mutually exclusive, and they are often used together. In fact, chemo and radiation have gotten a new lease on life as immunotherapy boosters. As these old standbys kill cancer, the dying cells release antigens that can spur immune cells into action, turning cold tumors hot.

Despite the barriers, the shift to more personalized treatment beyond chemotherapy is underway—but, like all things in evidence-based medicine, big changes take time.

“Our goal is for accessible treatments that provide longer lives with fewer symptoms for our cancer patients,” says Jackman. “And for many patients, chemotherapy still plays an important role in helping them live longer and feel better. That said, we are continually searching for newer and better ways to help our patients. With any new therapy, it takes time to develop these treatments, assess their safety and understand when and how they are best used.”

As paradigms change, it’s important to work with your health care team to explore different treatments. Ask if genomic testing and clinical trials might be right for you. Learn about all the available options—not just the most widely used—and don’t be afraid to seek a second opinion.

Personal Experience

“The ultimate goal,” says Lie, “is to be able to implement personalized medicine: a customized treatment regimen for each individual patient based on a thorough genetic analysis of their cancer, such that each patient is given the exact treatments they are most likely to respond to.”

Megan-Claire ChaseCourtesy of Megan-Claire Chase

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—Megan-Claire Chase (Warrior Megsie)

Kelly Shanahan, MDCourtesy of Kelly Shanahan, MD

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