ANTOINE DORE

A hopeful revolution in cancer care

Tissue-agnostic drugs that target genetic features rather than tissues have begun to reach some people with cancer. But these early successes might prove to be the exceptions. **By Julianna Photopoulos**

Since chemotherapy was first used to treat cancer in the 1940s, tumours have been tackled according to their organ or tissue of origin. Drugs used for breast-cancer therapy, for example, might be different from those used for lung or colorectal cancers.

In the past few years, however, clinicians have begun to use a new approach. Cancer is now being defined and treated in a more personalized and precise way — tumour genomes are sequenced so that people receive drugs matched to the genetic profile of their cancer cells. In 2017, the US Food and Drug Administration (FDA) approved the first tissue-agnostic drug for cancer — a treatment effective against tumours with a specific genetic alteration, regardless of the cancer's location. Two more tissue-agnostic drugs followed, in 2018 and 2019. "It's changing all of oncology," says Razelle Kurzrock, an oncologist and director of the Center for Personalized Cancer Therapy at the University of California, San Diego.

Making the link

But experts disagree on how far this approach can be taken. "A super small percentage of people actually have their treatment changed as a result of a tissue-agnostic approval," says Vinay Prasad, a haematologist–oncologist at the University of California, San Francisco. Although the drugs might be beneficial to some people with rare cancers, most cancers are not identified by a single genetic change. And even when researchers find molecular abnormalities that are common to tumours in multiple parts of the body, treatment might still have to be adjusted to take into account other differences between and in tissues.

In 2012, cancer geneticist Bert Vogelstein was visited in his laboratory at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University in Baltimore, Maryland, by a colleague with a puzzling observation. A drug that was producing dramatic responses in people with advanced skin and lung cancers, but that seemed ineffective against other cancers, had unexpectedly worked in a woman treated for colorectal cancer. The colleague wanted to know why. "A light bulb went off," says Vogelstein. Because both skin and lung tumours are notable for their extraordinarily large numbers of genetic mutations, he surmised that the woman's colorectal tumour had a DNA mismatch repair deficiency (MMR-D) — an inability to fix damaged DNA that results in hundreds to thousands of mutations in coding regions, especially in repetitive DNA regions known as microsatellites.

Testing revealed Vogelstein's hypothesis to be correct. The drug that had been used, nivolumab, works by inhibiting a protein found on the immune system's T cells, called programmed cell death protein 1 (PD-1). This action releases the brakes on the immune response to tumours. Further investigations by Vogelstein's group suggested that tumours with mismatch repair defects are particularly sensitive to such 'checkpoint inhibitors', because these cancers produce vast amounts of foreign antigens that the immune system has not encountered before, which can trigger a response. "We were super excited about this idea," he says. MMR-D is found in tumours in numerous areas of the body, so any drug that takes advantage of the deficiency has the potential to work in hundreds of thousands of people in the United States alone.

To test the idea further, Vogelstein and his team turned to another anti-PD-1 drug: pembrolizumab, which was initially approved for use in skin cancer in the United States in 2014. He gave the drug to people with colorectal cancer[1] — both those with and without MMR-D — as well as to people with MMR-D cancers in other parts of their bodies[2]. As expected, those with colorectal cancers without MMR-D did not respond, but the majority of people with MMR-D tumours did — regardless of where their tumours were located. "It was obvious from the first patient that it was having a dramatic effect," says Vogelstein.

The study was 1 of 5 clinical trials, involving a total of 15 tumour types, that led to the landmark FDA approval of pembrolizumab as a tissue-agnostic cancer treatment in 2017. The drug can now be given to adults and children with cancers that have either spread or which cannot be surgically removed, and that display evidence of MMR-D.

In June, the FDA approved another, even broader, indication for pembrolizumab: advanced solid tumours with high levels of genetic mutations. The drug can be used even if the reason for the high number of mutations is unknown, provided all other treatment options have been exhausted. With this approval, a high tumour-mutation burden is now used to predict who is likely to benefit most from immunotherapy. "It's the single best biomarker we have for immunotherapy responses," says Kurzrock. But the most common types of cancer in the study that led to this broader approval[3], including small cell lung cancer and cervical cancer, already have a path to PD-1 inhibition through pre-existing immunotherapies, argues Prasad. "It's not clear that the approval adds much," he says.

The threshold for a high mutation burden is at least 10 mutations per 1 million bases. This was set by the drug's manufacturer, Merck in Kenilworth, New Jersey. However, this cut-off is not absolute. "You're getting into the grey zone," says Vogelstein. For a start, what constitutes a high level of mutations can differ depending on the location of the tumour. Moreover, measurements can vary between labs and companies, says Kurzrock, and, although small, these variations might be the difference between whether a person qualifies for treatment or not. "There's a need to harmonize that read-out," she says. There is currently a US initiative to make these biomarker tests consistent and reproducible, she points out.

Scientists also disagree on whether pembrolizumab's most recent approval should have been given at all[4,5]. The correlation between response rate and tumour-mutation burden is thought to be continuous, rather than having specific thresholds[6]. And for some cancers, immune checkpoint inhibitors do not work, no matter what the level of mutation burden. Some also worry that the approval, which was based on an overall response rate of 28%, will mean that people could miss out on receiving other second-line therapies shown to increase survival. But Kurzrock says that half of the people in the trial that led to the approval continued to show a response for at least two years, which makes pembrolizumab a promising drug. "Very durable responses are something that we almost never see in solid tumour oncology," she says.

Mutation milestone

Unlike pembrolizumab, the two tissue-agnostic drugs approved in 2018 and 2019 act not on immune cells, but directly on tumours. Both larotrectinib (developed by Loxo Oncology in Stamford, Connecticut, and Bayer in Leverkusen, Germany) and entrectinib (made by Roche in Basel, Switzerland) target any advanced solid tumour with a genetic alteration known as a *NTRK* gene fusion, in adults and children. "It's a milestone in precision oncology," says Alexander Drilon, a medical oncologist at Memorial Sloan Kettering Cancer Center in New York City who was involved in clinical trials of both drugs.

NTRK genes make TRK proteins that are essential for the development and survival of certain nerve cells. *NTRK* gene fusions are unusual, occurring in less than 1% of common cancers, but are found much more frequently in rare cancers, such as secretory breast cancers and infantile fibrosarcoma.

What is unique about larotrectinib and entrectinib is the high response rates, regardless of which *NTRK* gene fusion is being targeted, the tissue or the person's age, says David Hong, an oncologist at the University of Texas MD Anderson Cancer Center in Houston, who was involved in clinical trials of larotrectinib. "In my career, I've never seen responses like this in advanced solid tumours per se without multisystemic chemotherapy," he says. However, sceptics of tissue-agnostic cancer drugs argue that the rarity of these mutations means that larotrectinib and entrectinib will never help more than a small number of people.

Another limitation of targeted therapies is resistance. "Cancers have their own defences," Vogelstein says. "They mutate just like normal cells do, and those mutations are going to eventually cause resistance." Drugs can be effective against different variants of the same gene, but different gene variants can become resistant to the same drug. Such resistance was seen in ten people during three clinical trials of larotrectinib, and the disease progressed in all ten[7].

Drilon is now testing next-generation TRK inhibitors such as selitrectinib and repotrectinib. These drugs are designed to target acquired mutations in the kinase domain of a protein when a tumour has developed resistance to targeted therapies. "The hope is that we will now see the tissue-agnostic approval of these next-generation therapies so that patients are able to get these drugs commercially," says Drilon.

Exception or rule

Even when drugs are a good match for a specific mutation, however, they do not always work. A prime example is a drug developed to target the gene *BRAF*, which promotes tumour growth and the development of new blood vessels.

BRAF mutations are most commonly found in melanoma, and people with this cancer often respond very well to *BRAF* inhibitors. Although the mutations also occur in around 10% of colorectal cancers, *BRAF* inhibitors have little effect against these tumours. "The site of the tumour makes a difference," says Ian Tannock, a medical oncologist at Princess Margaret Cancer Centre in Toronto, Canada.

The reason for this lies in the interaction between *BRAF* and the epidermal growth factor receptor (EGFR) signalling pathway. Inhibition of *BRAF* in colorectal cancer activates the EGFR pathway. This off-target effect results in drug resistance and cancer cells proliferating unimpeded. In melanomas, however, EGFR is expressed at low levels, and hence the drug works. "Tumour-agnostic drugs are only really going to be useful if the pathway they are targeting is the absolute dominant tumour-driver,"

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Research by Bert Vogelstein has led to the approval of tissue-agnostic cancer treatments.

says Julia Chisholm, a paediatric oncologist at the Royal Marsden's Oak Centre for Children and Young People in Sutton, UK.

Despite *BRAF* inhibitors not having a tissue-agnostic approval, Kurzrock points out that they have now received separate approvals for their use against multiple tumour types. This includes colorectal cancer – the FDA approved their use in combination with a second drug that targets the EGFR pathway in April. Kurzrock thinks this could become common for tumour-agnostic therapies; drugs that target a mutation that is present across multiple cancer sites will probably need to be used in combination with other agents, she says. Even melanomas respond better to a combination of drugs than to a *BRAF* inhibitor alone. "We should really move towards understanding why it didn't work and figure out strategies to develop better combinations, or better drugs altogether," Drilon says.

Unconventional trials

As genetic changes that can be targeted and that span multiple cancers have been found, clinical trials that test drugs across different tissues have begun. Known as basket trials, they allow people with different cancers to enrol in the same trial. However, they have attracted some criticism.

Basket trials broaden the pool of people with cancer that researchers can recruit from. But, because the target mutations are rare, recruitment is still a challenge, and sample sizes are usually small. For example, for larotrectinib, it took 15 types of genetic test and 2 years to enrol 55 people. As more people have their tumours genetically profiled, the number of available participants is likely to grow, says Hong. "It's still worth trying to find these patients."

Basket trials for tumour-agnostic therapies also typically lack a control group. It is unethical to have one, says Sandra Horning, an oncologist and co-founder of biotechnology start-up EQRx in Cambridge, Massachusetts. The people involved are often those without any other treatment options who will die very quickly without intervention. Drilon agrees: "If you have a drug that has a 75% response rate and you're requiring randomization to chemo that has a 30% response rate – would you really join a study like that?"

Prasad is less convinced by the efficacy of tissue-agnostic drugs, however. In 2018, he points out, only about 5% of people in the United States with metastatic cancer were found to benefit from a genomically targeted therapy[8]. He is also concerned that tissue-agnostic trials focus on how the tumour responds to a drug, rather than survival. "There's not a single approval that has a randomized control trial to show it actually benefits people with that aberration," he says. For example, larotrectinib was approved on the basis of data from 3 trials, involving 55 adults and children with 17 kinds of advanced cancer. It found that tumours shrank by 30% or more in 34 people and completely disappeared in 7. The overall response rate was 75%. For entrectinib, approval was based on 3 trials that cumulatively enrolled 54 adults and found an overall response rate of 57%. But "the response rate doesn't mean very much in terms of survival," says Tannock.

Instead, Prasad and Horning recommend using real-world data to evaluate the true effectiveness of tissue-agnostic therapies. Once a treatment is approved, its effects on survival can be measured using data in electronic health records. People with the same cancer who are not receiving the drug can act as the control group. Such post-approval analysis could also help health-technology assessment bodies to determine the cost-effectiveness of such treatments. For example, larotrectinib became the first tissue-agnostic drug to be approved by the European Medicines Agency in 2019. Initially, regulatory bodies in both the United Kingdom and Germany rejected the drug owing to its cost and a lack of evidence of benefit over existing treatments. However, the UK body later decided that the drug could be used for a probationary period, while more data are collected.

In the pipeline

Many tissue-agnostic drug candidates are in development. In January, the FDA granted priority review for selpercatinib, which targets the gene *RET*. But to extend the agnostic approach to the majority of cancers, some scientists think that they need to target more common mutant genes. For example, estimates suggest that up to 40% of all cancers have a mutation in the genes that encode RAS proteins – most frequently, *KRAS*.

Hong is involved in clinical trials with the experimental drug AMG-510, the first compound to successfully target the *KRAS* G12C mutation in solid tumours. So far, the drug has had promising results in lung cancer, with low toxicity, but for other cancers there is a very low or no response. "It looks a lot more like *BRAF* than it does *NTRK*," says Hong, who thinks that *KRAS* is unlikely to become a tissue-agnostic target in its truest sense. Although more targets are likely to emerge, he adds, some cancers will prove harder to crack than others, and will probably require treatment to be tailored to some degree.

Although tissue-agnostic drugs are unlikely to replace conventional treatment, they could still benefit some people. "It'll be an additional therapeutic arrow in our quiver," says Hong. Whether tissue-agnostic or not, Horning adds, approvals of these types of drug and their combinations are all about understanding the heterogeneity of the disease. "It's really just a step along the journey to better therapies," she says. "I do believe that the tissue of origin will continue to be important."

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