IMMUNOTHERAPY

Controlled attack

Immunotherapies such as checkpoint inhibitors unleash the body's ability to defend itself against kidney cancer.

BY CHARLES SCHMIDT

In 2013, Robert Motzer was treating a 71-year-old man with advanced kidney cancer who seemed to be at death's door. A medical oncologist at the Memorial Sloan Kettering Cancer Center in New York City, Motzer was recruiting patients for a phase I clinical trial for an especially promising treatment. The trial combined two immunotherapies called checkpoint inhibitors, which remove the brakes from the body's mechanism to kill growing tumours. Motzer's patient enrolled in the study and it saved his life. "He's still in complete remission," Motzer says. "I see him for maintenance treatments every two weeks and the question now is whether we can stop."

Immunotherapy is galvanizing research on kidney cancer. One of the drugs Motzer's patient took, a checkpoint inhibitor called nivolumab, was approved for advanced kidney cancer in the United States in November 2015 (and in Europe in April 2016). Nivolumab is the first drug to extend lifespan in people with kidney cancer who do not response to first-line treatment. Researchers are now trying to build on that success using a variety of new immunotherapies that they hope will prolong survival and perhaps even cure the disease.

These approaches each harness T cells, white blood cells often described as the immune system's foot soldiers. Deployed effectively, T cells can be 'trained' to kill off new metastases and prevent cancer from spreading to the brain and other organs. "T cells offer the dual advantages of being able to kill cancer cells and also to remember what they look like," says immunologist Marcela Maus at Massachusetts General Hospital in Boston.

Motzer shares Maus's enthusiasm for using immunotherapy to treat kidney cancer. "It's hard to get excited about other approaches," he says. "Newer immunotherapies are the most fascinating and promising kidney-cancer drugs on the horizon."

With 338,000 cases diagnosed in 2012, kidney cancer is the world's twelfth most common malignancy. It typically occurs in people aged 65 years or older, and, in the United States, it has a 5-year survival rate of between 75% and 81%. For the roughly 30% of patients with metastatic kidney cancer, however, the prognosis is considerably worse. For reasons that aren't well understood, kidney cancer doesn't respond well to chemotherapy or radiation.

In rare cases, kidney tumours regress spontaneously. Scientists, therefore, had speculated as long ago as the late 1800s that the cancer would be vulnerable to an immunological attack. The first immunotherapy in oncology to reach the market, was a recombinant form of interleukin-2 (IL-2), which was approved by US regulators in 1992 for advanced, metastatic kidney cancer. IL-2 is a cytokine, a protein involved in cell-to-cell communication. By increasing the populations of T cells and natural killer cells that can turn against tumours, it results in complete remission (the disappearance of all signs of cancer) for 5–10% of patients, some of whom have been cancer-free for decades. But IL-2 is also very toxic. The drug works best at high doses that commonly cause debilitating side effects, including nausea, vomiting, skin rashes, hypotension, gastrointestinal bleeding, diarrhoea and confusion.

In the mid-2000s, the treatment landscape broadened with the arrival of better-tolerated targeted therapies. The first were the anti-angiogenic drugs sorafenib and sunitinib. Both drugs inhibit receptors of vascular endothelial growth factor (VEGF, a protein involved in the formation of tumour blood vessels), and so deprive tumours of blood-derived nutrients. Two other targeted therapies — temsirolimus, approved in 2007, and everolimus, approved in 2009 — block the mTOR protein, which is

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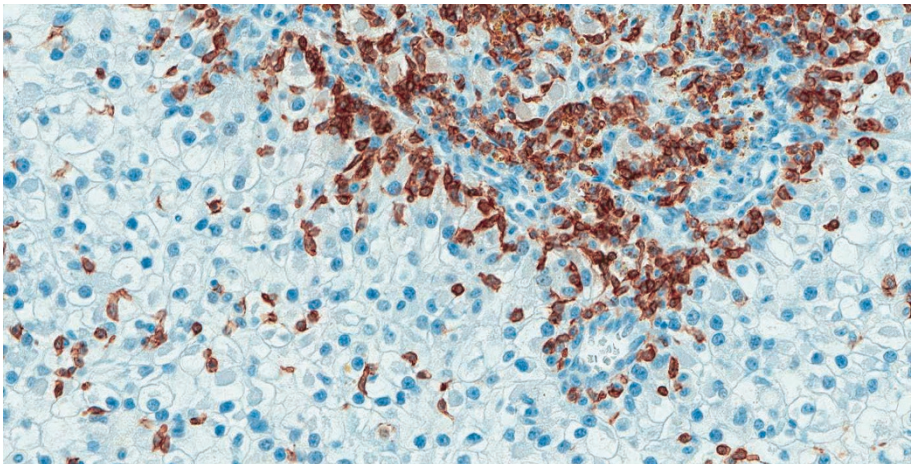

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T cells (stained red) infiltrate the clear-cell subtype of renal cell carcinoma.

involved in cancer-cell growth and proliferation (see page S106).

Targeted therapies improve kidney-cancer survival time, but they have a major drawback: tumours eventually become resistant to them. That's what happened to Motzer's patient at Memorial Sloan Kettering — sunitinib and everolimus had both stopped working before the patient began the nivolumab trial.

CHECKPOINTS AND COMBOS

According to Jorge Garcia, a medical oncologist at the Cleveland Clinic Cancer Center in Ohio, nivolumab is now the treatment of choice when targeted drugs no longer work. Nivolumab's target, a protein called PD-1, is an immune checkpoint that shuts down T cells before they harm normal tissues. T cells attack with such ferocity that they rely on checkpoints such as PD-1 to keep them under control. But tumours can exploit this mechanism to protect themselves. Located on T-cell surfaces, PD-1 attaches to a receptor called PD-L1 on cancer cells. That binding tricks T cells into no longer viewing tumours as foreign. Nivolumab blocks PD-1 from attaching to PD-L1, and thus exposes cancer cells to an immune attack.

Another checkpoint inhibitor on the market, ipilimumab, blocks a different protein known as CTLA-4. This checkpoint dampens immune reactions before they generate too much inflammation. By blocking CTLA-4, ipilimumab keeps T cells active, so that they can continue to recognize and kill cancer cells. But whereas nivolumab affects only T cells in the tumour, ipilimumab activates T cells indiscriminately throughout the body and, therefore, has more side effects. Because nivolumab is not as toxic as the CTLA-4 blocker, it can be given "to all types of patients, including older and sicker patients", says David McDermott, a medical oncologist at Beth Israel Deaconess Medical Center in Boston, Massachusetts.

Now in a phase III trial, researchers, including Motzer, are investigating the combination of nivolumab and ipilimumab for treating advanced kidney cancer. The rationale for the combination is that the two drugs work on different parts of the checkpoint cycle: CTLA-4 boosts T-cell activity whereas PD-1 and PD-L1 act on cells in the tumour's microenvironment. So far, preliminary results look promising, according to Motzer. "We've seen 40% response rates that are in many instances durable," he says. "And that's significant since we're going head-to-head with Sutent [sunitinib], which has been the standard front-line treatment for ten years." McDermott cautions that adding CTLA-4 inhibition to the mix comes with trade-offs. "It may add efficacy, but it's also more toxic," he says.

In another phase III clinical trial, investigators are combining the VEGF inhibitor bevacizumab and a checkpoint inhibitor called atezolizumab. The rationale in this case is that the slowdown in tumour growth from the antiangiogenic treatment might create more favourable conditions for immunotherapy. Instead of targeting PD-1, atezolizumab targets its receptor, PD-L1. Whether that is an advantage is up for debate. Dietmar Berger, head of oncology at Roche Pharma Development in San Francisco, California, which is developing atezolizumab, argues that blocking PD-L1 is safer because preclinical studies suggest that there is a lowered risk of autoimmune side effects. But McDermott cautions that, without comparable data, the advantages of targeting PD-1 compared with PD-L1 are speculative.

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A ROLE FOR VACCINES

Checkpoint inhibitors are the most advanced immunotherapies available for kidney cancer. But other approaches also look promising — especially cancer vaccines, according to Robert Figlin, an oncologist at Cedars-Sinai Medical Center in Los Angeles, California.

Cancer vaccines rely on a patient's tumour cells, or tumour-associated products, to boost immune reactions against a malignancy. Figlin is principal investigator on the ADAPT study, a phase III trial that is using a vaccine called AGS-003. To make the vaccine, scientists extract a patient's blood-borne dendritic cells — antigen-presenting immune cells — and expose these cells to RNA from the patient's tumour. The vaccine is re-introduced into the patient in the hope that the dendritic cells will stimulate the immune system to attack any new cells that bear the tumour's RNA signature.

So far, Figlin says, kidney-cancer vaccines have been unable to overcome immune resistance in the tissues around the tumour. To solve that problem, the ADAPT trial combines AGS-003 with the antiangiogenic drug sunitinib. Importantly for this application, sunitinib also suppresses certain types of white blood cells that limit immune responses, such as myeloid-derived suppressor cells and regulatory T cells. Results from a phase II study are encouraging: 13 of 21 patients showed a clinical benefit, although none had a complete response (A. Amin *et al. J. Immunother. Cancer* **3,** 14; 2015). Results from the phase III study, which has already recruited all its patients, are expected in mid-2017. "We've treated over 400 patients and haven't encountered any major safety problems," Figlin says.

What Figlin and others hope to discern is why some people with kidney cancer do better and have more dramatic responses with immunotherapy than others. Identifying biomarkers that predict likely responders is a priority for the field, especially with treatment costs per patient topping US$100,000 per year. So far, however, that search has been an exercise in frustration. "We still don't have a biomarker for kidney cancer that we can apply in clinical practice," Motzer says. Early hopes that PD-L1 levels in the tumour could be a candidate proved disappointing, adds McDermott, partly because PD-L1 is only transiently expressed. "If you sample the wrong part of the kidney, you might get a false-positive result." McDermott says that other potential biomarkers under investigation include the expression of $CD8^+$ T cells and the amount of tumour-infiltrating white blood cells in the kidney.

What is clear, McDermott says, is that the more aggressive and mutated a person's cancer, the better the odds are that immunotherapy will work. McDermott explains that this is because highly mutated cancers express more of the unusual antigens that attract an immune response. "We need to better understand which specific mutations are driving that immunity," McDermott says. "We want more durable responses and more people at the tail end of the survival curve. I'm less excited about improving median survival … than I am about seeing more patients in remission and off drug treatment." ■

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