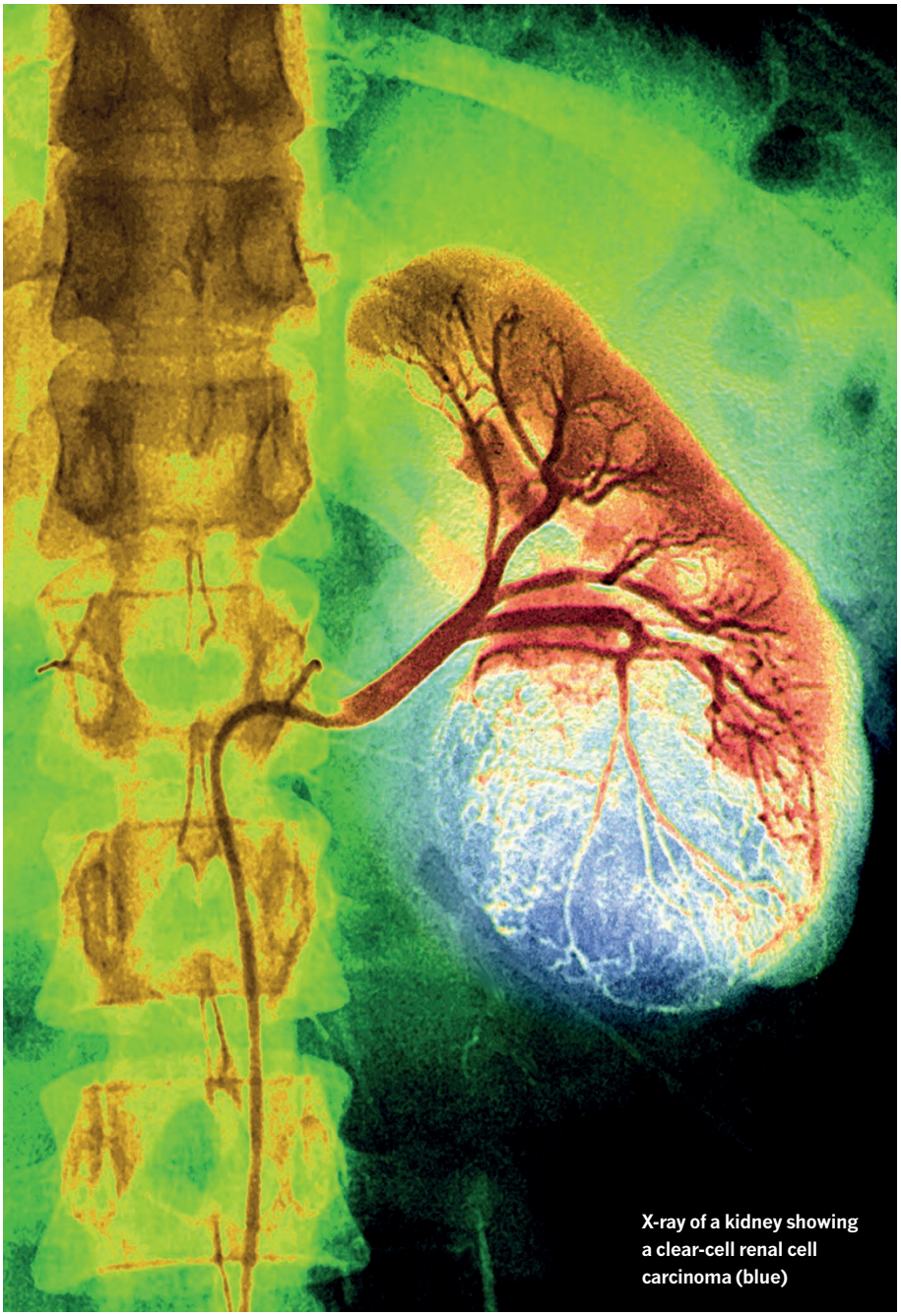

X-ray of a kidney showing a clear-cell renal cell carcinoma (blue)

SOVEREIGN/ISM/SPL

TARGETED THERAPY

An elusive cancer target

Advanced tumours may have met their match with new drugs, but why have these treatments proved ineffective at stopping early-stage tumours from coming back?

BY CAROLYN BROWN

Kidney cancer has frustrated the best efforts of clinicians. The disease is notoriously resistant to chemotherapy, and is often caught only after it has metastasized. As recently as 2013, survival for people with advanced cancer who were treated in clinical trials was two and a half years on average.

"I've been here taking care of people with kidney cancer for over 25 years," says Robert Motzer, a medical oncologist at the Memorial Sloan Kettering Cancer Center in New York City. "When I started here in the 1980s, the average survival on chemotherapy was less than a year."

Treatment advances were modest over the intervening decades. But in the past year, three new drugs have brought hope. These therapies represent the "first big revolution that is going to change survival and the way we are going to treat our patients", says Bernard Escudier, a kidney-cancer specialist at Gustave Roussy near Paris. The key developments revolve around research on the genetic changes that allow kidney tumours to create their own blood supply and grow. The new drugs target the specific pathways in the process, and hold promise for personalized therapy that is more effective, and has fewer side effects, than previous treatments. "The paradigm has changed with these new drugs all coming in within a year," says Motzer.

But it is a revolution that seems to have passed by early-stage kidney cancer. Targeted therapies do not prevent initial tumours from recurring and can have serious toxic effects. This 'good news, bad news' story, however, is teaching researchers more about how the disease works.

AMBUSHING CANCER PATHWAYS

Targeted therapy arose from the discovery that a gene called *VHL* is inactivated in most people with clear-cell renal cell carcinoma (RCC), which accounts for about 70% of kidney cancers. When it is functioning, VHL suppresses tumours by regulating angiogenesis — the formation of new blood vessels. Tumours need their own blood supply to grow, the loss of VHL allows this angiogenesis.

Researchers have been exploring the promise of drugs that treat cancer by stopping angiogenesis since the process was first proposed in 1971 by the US vascular researcher Judah Folkman. The first antiangiogenesis drug for any type of cancer, bevacizumab, was approved in 2004 for metastatic colon cancer. The drug has since been approved for a variety of cancers, including advanced RCC. The first antiangiogenesis drugs approved specifically for RCC, sorafenib and sunitinib, were approved in 2005 and 2006. "It changed the way we treated this disease, away from

© 2016 Macmillan Publishers Limited, part of Springer Nature. All rights reserved.

A NEW ERA OF TREATMENT

Targeted drugs have changed the approach to the treatment of kidney cancer. The most recent approvals are giving patients an even better chance of survival.

Drug	Brand name	Pathway targeted	US Food and Drug Administration approval for RCC*	European Medicines Agency approval for RCC*
Sorafenib	Nexavar	VEGFR	2005	2006
Sunitinib	Sutent	VEGFR	2006	2006
Temsirolimus	Torisel	mTOR	2007	2007
Everolimus	Afinitor	mTOR	2009	2009
Bevacizumab	Avastin	VEGF-A	2009	2008
Pazopanib	Votrient	VEGFR	2009	2010
Axitinib	Inlyta	VEGFR	2012	2012
Nivolumab	Opdivo	Checkpoint inhibitor (PD-1)	2015	2016
Cabozantinib	Cabometyx	VEGFR, MET and AXL	2016	Not yet approved
Lenvatinib	Lenvima	VEGFR	2016	Not yet approved

*Drugs may have been previously approved for other types of cancer.

chemotherapy and towards these targeted drugs," says Motzer. "It opened up a whole new era of treatment."

Sorafenib and sunitinib opened the floodgates. In the next ten years came pazopanib and axitinib (see 'A new era of treatment'). Each of these drugs targets the tyrosine kinase receptors of an enzyme involved in the growth of blood vessels, vascular endothelial growth factor receptors (VEGFRs). In spring 2016, two more VEGFR inhibitors, cabozantinib and lenvatinib (in combination with everolimus), were approved by the US Food and Drug Administration (FDA) for the treatment of RCC. These newly approved drugs are more effective than their predecessors, increasing the time before the cancer progresses as well as improving survival. This might be because the drugs target other pathways in addition to VEGFR, says Motzer.

Another new class of drug targets a different enzyme linked to angiogenesis, known as mTOR. Temsirolimus and everolimus were approved for advanced RCC by the FDA in 2007 and 2009, respectively.

A third pathway involves a molecule made by many types of cancer cell: the ligand PD-L1 binds to a receptor called PD-1 on immune cells known as T cells and stops these cells from attacking the cancer. Nivolumab was approved for advanced RCC in November 2015. The checkpoint inhibitor blocks PD-1 on T cells, allowing the cells to find and kill the tumour (see page S109).

PROMISE AND PROBLEMS

Until the past-year's entrants on the scene, this plethora of new drugs had positive, but mixed, results. Motzer has led randomized trials of several of these drugs, and found that survival generally improved. Pazopanib and sunitinib increased average survival time to two and a half years[1]. "Patients have their disease controlled for a certain time period and then generally progress," Motzer says. "We see very few complete remissions."

The outcomes have disappointed Naomi Haas, who specializes in kidney and prostate cancer at the University of Pennsylvania's Abramson Cancer Center in Philadelphia. The initial rush of excitement following the drugs' approvals has faded, she says. "As time went on, we realized the drugs had a lot of side effects and it was a small proportion of people who had complete disappearance of their cancer."

And the drugs do not work for early-stage tumours. If RCC is caught before it has spread beyond the kidney, the survival rate is very high. Unfortunately, because early-stage tumours rarely cause pain or significant bleeding, they are usually found by accident, after diagnostic imaging for other reasons. If tumours are not caught early, they are often not detected until the cancer has metastasized.

For early-stage tumours, the main treatment is surgery. Part or all of the kidney is removed, depending on the extent of the tumour. The nearby adrenal gland and lymph nodes may also be removed. Follow-up involves observing the kidneys for recurrence or spread. Clinical trials of chemotherapy, hormonal therapy and immunotherapy with interleukin-2 or interferon have all shown no difference in recurrence of tumours.

Using prediction tools called nomogram tables, clinicians can assess the risk of recurrence. The table can include criteria such as the tumour's stage at the time of surgery, the patient's status (extent of symptoms or physical-activity level, for example), the tumour's grade (based on the Fuhrman grading system) and the presence of tumour necrosis. Tumours are considered to be high risk if, according to the criteria, the chance of recurrence is 40% or more.

In a study earlier this year, Haas investigated the effectiveness of the antiangiogenesis drugs sunitinib and sorafenib for people with early-stage RCC who are at high risk of recurrence[2]. Because these drugs halted the progression of advanced cancer, the hope was that they would also prevent it from reoccurring. But that was not the case. "I was very surprised to see that in our hazard ratio, the curves were virtually the same as placebo," Haas says.

The study was stopped earlier than planned. The time to recurrence in the people who were treated with the drugs after the initial tumour was surgically removed was not significantly different to the placebo group. The question is why? Haas thinks that the answer will help researchers to better understand how RCC spreads.

"Patients have their disease controlled for a certain time period and then generally progress."

The targeted therapy may not have worked for early-stage RCC because, compared with large, highly vascularized metastatic tumours, the 'micrometastases' that establish new tumours when the disease reoccurs may not yet have their own blood supply, Haas explains.

The drugs also caused more-severe side effects in early-stage patients than had been seen in patients with advanced cancer. These were mainly hypertension, hand–foot syndrome (calluses on hands and feet that can become raised and tender), rashes and fatigue. It is not clear why there is a higher rate of serious side effects in people with early-stage cancer, Haas says. Although the people in her study may have been healthier than later-stage patients and so have simply noticed and reported more side effects, Haas thinks that the drugs may cause worse side effects when there are no tumours. "These drugs have no tumour to hit, so they may have more 'off-target' effects," she says. "They're hitting normal organs and making people feel worse."

© 2016 Macmillan Publishers Limited, part of Springer Nature. All rights reserved.

MEMORIAL SLOAN KETTERING CANCER CENTER

Robert Motzer, a medical oncologist at the Memorial Sloan Kettering Cancer Center.

Escudier says that trials are underway to investigate other VEGFR inhibitors in early-stage RCC, but he is not hopeful. "It is very likely that all of these trials are going to be negative," he says. These drugs have also failed in other types of cancer such as breast and colorectal cancer, Escudier says. The negative results of Haas' study were "not a surprise", he says.

SHIFTING STANDARDS OF CARE

But there is good news. Antiangiogenesis drugs have changed the standard of care for advanced RCC, increasing lifespan with a reasonable quality of life for patients.

Following a shift, initially from chemotherapy to immunotherapy and then towards antiangiogenics, the recommended protocols for which drugs to use in which sequence also changed, as new drugs moved from lab to bedside. Up to four lines of defence against RCC are needed because, in most cases, tumours eventually develop resistance to drugs that target a particular pathway. The strategy is to switch drugs — and often pathways — until the cancer eludes the therapy.

Protocols can vary, but first-line treatment will involve either an immunotherapy, a VEGFR inhibitor or an mTOR inhibitor. Once resistance develops and cancer progresses, patients are switched to another therapy — either a different VEGFR or mTOR inhibitor or the checkpoint inhibitor nivolumab.

But Motzer has achieved promising results by combining drugs to target three pathways at once[3]. He used lenvatinib, which targets both VEGFRs and fibroblast growth factor receptor (also thought to be involved in angiogenesis in RCC), combined with everolimus, which targets mTOR. The combination led to improved survival — both before the cancer progressed and overall — than everolimus alone. Although Motzer had hoped for an improved result, he was surprised at the magnitude of the improvement: the drug combination prevented cancer from progressing for a median of 14.6 months.

"We do not know for certain why the results were so good."

The phase II trial led to FDA approval of lenvatinib with everolimus for advanced RCC. Motzer is now planning a randomized controlled trial that compares lenvatinib in combinations with two other drugs, with sunitinib as a control.

Motzer, along with Escudier, also found that cabozantinib led to longer survival than everolimus[4]. "We do not know for certain why the results were so good," says Motzer. In addition to inhibiting VEGFRs, cabozantinib inhibits its two other tyrosine kinases, MET and AXL, which are found at high levels in people with clear-cell RCC and are associated with a poor prognosis. The interaction with these proteins may account for the results, says Motzer.

PERSONALIZED THERAPY

The new therapies make the protocols for treatment a moving target. Escudier says that the priority for research now is to determine how to select the best therapy for the patient. "We really need to know how to use the drugs we have." For example, if one drug works for about 30% of patients, how do you identify the 30% that should be given the drug?

Although patients are currently stratified for therapy, according to their risk of recurrence, stage of cancer and previous treatments, the promise of personalized therapy is that treatments can be aimed at a pathway specific to the individual's cancer — selecting the right drug for the right patient.

Instead of bombarding RCC with drugs that target several pathways, in the future, the target will be determined first. "Probably, in the very near future we are going to treat only those patients who have an mTOR aberration in the pathway" with mTOR inhibitors, Escudier says.

But to decide the best therapy, clinicians need something that they can test for to tell them which is the relevant pathway. This can include biomarkers or genomic and next-generation sequencing methods to determine the phenotype of the tumour, Escudier says. Over the next few years, results should be available from studies examining the selection of therapy based on the tumour phenotype. Personalizing therapy would not only be more effective, but would also help to avoid the accumulated adverse effects of taking several drugs at once.

Researchers also need to understand how long drugs need to be given and at what dosage. "We want to give them as much as we need to — not too much — to avoid toxicity and keep the efficacy," says Escudier.

The promising outcomes of targeted therapies are changing the treatment goals for people with advanced RCC. Clinicians used to talk in terms of progression-free survival (how long until the cancer progressed) and overall survival (how long until the patient died). Now, they are daring to talk about the disappearance of the cancer. Escudier thinks that complete remission may be achievable in 20–30% of patients in the next few years, on the basis of the rates of response to the new drugs and the increasing rates of survival that have been reported.

The incremental improvements in patients' survival have been double-edged, says Escudier. "You see your patients more frequently and you become friends with them, yet in the end they die." It is frustrating to be unable to offer a cure, he says. With new treatments and improved prognosis, Escudier is looking forward to giving them better news. ■

Carolyn Brown *is a freelance writer based in Ottawa, Canada.*

1. Motzer, R. J. *et al. N. Engl. J. Med.* **369,** 722–731 (2013).
2. Haas, N. B *et al. Lancet* **387,** 2008–2016 (2016).
3. Motzer, R. J. *et al. Lancet Oncol.* **16,** 1473–1482 (2015).
4. Choueiri, T. K. *et al. N. Engl. J. Med.* **373,** 1814–1823 (2015).

© 2016 Macmillan Publishers Limited, part of Springer Nature. All rights reserved.