New advances deliver fresh hope in kidney cancer

Pharmaceutical companies have made important inroads in the treatment of renal cell carcinoma, and a continued understanding of the genetic drivers underlying the disease and validation of new targets should lead to further benefits for patients, reports Malini Guha

Oncologists widely agree that there has been a genuine revolution in the treatment of renal cell carcinoma (RCC), a traditionally underserved and difficult-to-treat tumour which accounts for about 90% of cases of kidney cancer.

In the last several years, four new "targeted" anticancers have been approved to treat RCC after showing a benefit – an unprecedented number in such a short span of time. Median survival of newly diagnosed patients with advanced/metastatic RCC may have doubled to over two years with the use of just one drug, and may be lengthened further when the drugs are used sequentially. As a result, survival in RCC looks to have improved by more than for any other major cancer in these few years.

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Until just a few years ago, there were only a couple of drugs used to treat RCC – the natural immune system molecules interferon-alfa and interleukin-2 (IL-2). The former had modest benefits while the latter, which comes with substantial toxicity, resulted in long-term cures for a minority (about 5%) of patients.

Meanwhile, chemotherapy and radiotherapy did not appear to work at all in the disease, whose incidence has unfortunately been rising steadily (by about 2% each year) in the Western world over the last few decades, and is in the top 10 biggest cancer killers. Partly because of the dearth of effective therapies, median survival for patients with advanced RCC was one of the worst in cancer – about 12-14 months.

The success of the drugs that have been approved in the past few years in RCC appears to be due to the fact that they are targeting a fundamental genetic driver in the disease – which may not be the case in the other tumour types in which they have been tested so far – and serves as a lesson for future drug development in both RCC and other cancers.

"We have patients who are now living five years with metastatic renal cancer who were in the original trials of the new drugs. Those patients have always existed, but there are far more of those now – they are a much more significant minority than in the past," says Dr Walter Stadler, director of the genitourinary program at the University of Chicago Medical Center. "Previously, the vast majority of patients had absolutely no benefit with any therapy. Now we have drugs where maybe two thirds to three quarters have major benefits."

Yet, none of these drugs represents a cure, and median survival for patients with advanced RCC is still under three years. "We still can't put down our guard or turn our weapons in," says Dr Primo Lara of the University of California Davis Cancer Center.

In order to further improve survival, cancer doctors and researchers recommend a number of avenues of further investigation. First, they emphasise that the biology of RCC must be more fully understood and drugs developed to hit new targets and pathways in the cancer cell that are shown to be important in driving the disease.

Then, as different patients' tumours may have different genetic drivers, biomarkers must be validated to predict which patients are likely to respond to a particular targeted therapy. This "personalised medicine" approach would improve the outcomes of many patients while saving others from unnecessary treatments which are costly and come with side-effects.

The high cost of the drugs, in the tens of thousands of dollar range each year, has led to significant controversy. In the UK, for example, where they cost more than £3,000 for a six-week cycle, the National Institute for Health and Clinical Excellence (NICE), which assesses technology for the National Health Service in England and Wales, in its draft appraisal last August deemed the drugs not to be cost-effective. It recently, however, changed its view on one of the drugs, Pfizer's Sutent (sunitinib). This followed its adoption of new rules for end-of-life drugs, which can sometimes be recommended now even if they represent a cost of more than £30,000 per quality adjusted life year.

And while the expense of combinations of targeted drugs may be even more formidable, many doctors believe that they may improve outcomes compared with monotherapy, akin to combination chemotherapy. This is either because more than one pathway needs to be inhibited, one drug will fail to completely block a key pathway on its own, or resistance to a single drug is more likely to arise than to a combination. Another approach when resistance arises to one drug is sequential therapy – and in order to determine the most appropriate sequences of the targeted drugs, the mechanisms of drug resistance should be uncovered.

Drugs must be also be tested after removal of a localised tumour (known as the adjuvant setting) to prevent disease recurrence, which unfortunately is common in RCC – about 40% of patients who initially appeared to be cured by surgery recur and develop metastatic disease. The adjuvant setting is one in which a true cure – rare in metastatic disease – is possible, and therefore the cost/benefit ratio of the drugs may significantly improve for these patients.

Finally, as treatment with high-dose IL-2 has led to miracles in a small percentage of advanced RCC patients, the use of immunotherapy should continue to

be explored in the disease. However, with numerous failures in this area of research over the past couple of decades, more must be understood about the patients and settings in whom this approach might work best.

the new drugs

Starting in 2005, four new drugs have been approved to treat advanced RCC. Bayer/Onyx Pharmaceuticals' Nexavar (sorafenib) was the first, and was tested in its pivotal trial in the second-line setting, after patients had failed treatment with interferon-alfa or IL-2. It doubled median progression-free survival (PFS; the length of time during and after treatment in which the cancer does not progress, or grow) compared with placebo.

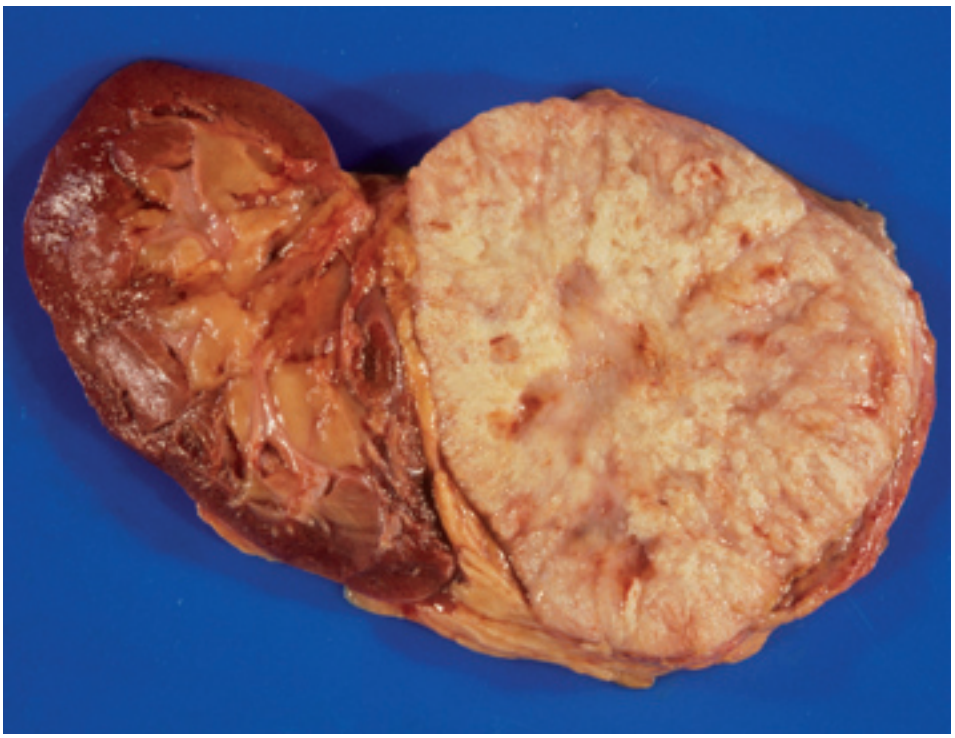
The next year, Pfizer first launched its rival drug Sutent, which was approved based on a trial in newly diagnosed advanced RCC patients in which it more than doubled median PFS compared with interferon-alfa. Sutent now appears to be the most commonly prescribed first-line treatment in RCC and last year had sales of $847 million.

In 2007, Wyeth's Torisel (temsirolimus) was launched after also being tested as an initial therapy – in a subgroup of poor prognosis patients – where it prolonged median survival by about three months compared with interferon-alfa.

Finally, last year Roche/Genentech's Avastin (bevacizumab) was approved in the EU after also being tested as an initial therapy (in combination with interferon-alfa), and it is awaiting US approval. Avastin plus interferon almost doubled median PFS compared with interferon, similar to Sutent, while overall survival data are not yet available.

Additionally, Novartis recently filed for US and EU approval of its competitor to Torisel, Afinitor (RAD001; everolimus), after testing it in heavily pretreated patients who had few other options. Afinitor more than doubled median PFS compared with placebo.

In most of the trials, many patients in the control arm (interferon-alfa or placebo) crossed over to the experimental arm when the PFS benefits were observed with the new drugs, or they received treatment with the new drugs after the ends of the trials. This makes it difficult to compare overall survival between the arms of the studies.



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FUTURE R&D: Cancer experts are pushing for improved understanding of the biology of renal cell carcinoma and robust biomarkers to facilitate personalised medicine approaches

Therefore, doctors look to the median overall survival seen in trials with interferon in newly diagnosed advanced RCC patients – 12 to 14 months – to judge better the benefits of the new therapies. Median survival with Sutent in this setting was 26 months. PFS is also commonly used in cancer drug trials as a surrogate for overall survival, so that a doubling of PFS would likely lead to a significant survival benefit.

key to success

Some of the newly marketed drugs for RCC have been tested in several other major solid tumours, but have not shown as large a magnitude of benefit as in RCC, or have failed outright. For example, Avastin resulted in a two-month median survival benefit in one Phase III trial in non-small cell lung cancer (NSCLC) and no survival benefit in another. Nexavar also failed to prolong survival in one Phase III trial in NSCLC, while Torisel failed a Phase III trial in breast cancer.

The reason for greater success in RCC, doctors believe, is that the drugs are targeting a fundamental genetic driver of the cancer – at least one key to the disease looks to have been found.

Many genes that are commonly mutated in other solid tumours, like the tumour suppressor p53 and the oncogene Ras, are not seen to be frequently mutated in RCC. On the other hand, the VHL tumour suppressor gene (discovered 15 years ago), which is not commonly mutated in most other tumour types, is found to be defective or lost in the majority of RCC tumours.

About 70-80% of cases of clear-cell RCC are characterised by defects in VHL. Clear-cell RCC comprises about 75% of cases of RCC, and is generally the most aggressive form (about 90-95% of metastatic tumours are clear-cell RCC) and where most of the new drugs have been tested.

The best understood target of the VHL protein is the HIF protein, a transcription factor implicated in the control of genes that are turned on by low oxygen (hypoxia). VHL only targets HIF for destruction in the presence of oxygen. In hypoxic conditions or in tumour cells lacking normal VHL protein, HIF accumulates and activates genes that promote survival in a low-oxygen environment. Among these are those that direct the synthesis of proteins that induce new blood vessel formation (angiogenesis), including vascular

endothelial growth factor (VEGF), TGF-alpha and beta, and PDGF-B. VEGF is thought to be the major mediator of tumour angiogenesis and signals mainly through the VEGFR2 receptor. Angiogenesis, which supplies the tumour with nutrients and oxygen for its continued growth, is a key process in the development of cancer.

Of the four recently approved drugs in RCC, three directly target the VEGF pathway (Avastin targets VEGF, while Sutent and Nexavar target VEGF receptors amongst numerous other protein kinases). As inhibiting mTOR has been shown to inhibit production of HIF, the mTOR inhibitor Torisel also likely decreases levels of VEGF.

"The targeted agents in RCC are targeted towards a critical pathway in tumour development, driven by VHL and its downstream effects," says Dr Robert Figlin, an oncologist at the City of Hope National Medical Center in California. "In other cancers, it may be the secondary effect of tumour growth leading to the hypoxic environment which stimulates angiogenesis."

"We found a key for the disease, drugs that inhibit tumour-associated blood vessels is the correct approach. The biology is correct in terms of the targets we are focusing on," agrees Dr Ronald Bukowski of The Cleveland Clinic in Ohio. In terms of its appearance, RCC is an unusually vascular tumour, and it bleeds easily.

The success of the anti-angiogenic drugs in RCC highlights, along with the examples of Novartis's Gleevec (imatinib) in chronic myeloid leukaemia and Roche/Genentech's Herceptin (trastuzumab) in HER2-positive breast cancer, the necessity to identify with precision the underlying genetic drivers in different tumour types, and tumour subtypes, in order to make a significant impact on survival.

new targets

The successes of Sutent and Nexavar have stimulated many companies to try to improve upon them, so that drugs targeting the VEGF receptors are amongst the most represented in the Phase II and Phase III pipeline in RCC.

Dr Robert Motzer, an oncologist at Memorial Sloan-Kettering Cancer Center in New York, says he hopes the next generation of the VEGFR-targeted drugs come with better efficacy or tolerability. Pfizer's follow-on to Sutent, axitinib – which is being compared with Nexavar in a Phase III trial in the second-line setting – is more selective for VEGF receptors than Sutent, which hits many additional protein kinases. Whether axitinib represents an improvement over the first-generation VEGFR-targeted drugs may depend partly on whether the other kinases which the latter drugs inhibit are relevant to RCC, says Dr Motzer. GlaxoSmithKline is also pitting its VEGFR-targeted drug pazopanib (Armala) against Sutent in a first-line Phase III trial hoping to demonstrate a survival advantage.

However, VEGF is not the only logical target in RCC and it is unlikely that the new drugs in development which target this pathway will result in the next quantum leap in survival, even if they show some additional benefit.

"We need to continue to understand the biology of RCC, and the new drugs need to be based on scientific rationale – I don't hope that a better-targeted VEGF agent will win, we should look for new targets and pathways," emphasises Dr Figlin. "The target is RCC, not VEGF."

Dr Motzer agrees: "We need more intensive study in RCC to identify more targets. I hope the excitement in RCC due to the clinical success stimulates tumour biology studies."

As co-director of the Wellcome Trust Sanger Institute's Cancer Genome Project, Dr Andy Futreal has been analysing thousands of genes in hundreds of RCC tumour samples from patients to see whether any gene besides VHL is commonly mutated in the disease. In a screen of the coding sequences of 4,000 of the approximately 22,000 genes in the human genome, he says that nothing even approaching VHL has been found. However, some genes have been found to be mutated in about 2% of samples, and appear to play a function role in these tumours. This disease heterogeneity, he admits, poses a hurdle for drug development.

"There are a reasonable number of infrequently mutated genes in RCC – it is not how one would want it to play out." Nevertheless, Dr Futreal adds, "Finding all the genes that are mutated in a given cancer type will point us towards pathways, towards targeting pathways rather than a gene-centric approach necessarily."

Additionally, he says, there may be more frequently mutated genes in RCC found, or major gene rearrangements such as chromosomal translocations, when his team analyses the rest of genome. "We haven't written off the idea yet that there are other major drivers in RCC other than VHL," Dr Futreal says.

For now, absent any other major smoking gun in RCC, it still makes good sense to focus on VHL and its effects, and these are not limited to angiogenesis and increased levels of VEGF.

"We do need to think about targeting other components of the VHL pathway – VHL affects cell proliferation, glucose metabolism… We have some understanding of the pathways, but our understanding is still incomplete," Dr Stadler admits.

VHL has other HIF-independent functions, "but we don't understand the biochemistry of these functions", agrees Dr William Kaelin of the Dana-Farber Cancer Institute and Harvard Medical School, who has focused much of his attention on studying the gene.

HIF also has numerous effects, he says, which are not just related to angiogenesis. For example, the growth factor TGF-α is upregulated by HIF, and can bind to the epidermal growth factor receptor (EGFR) on the cell surface and stimulate cell proliferation, which is of course another key process in cancer.

Some EGFR-targeted drugs on the market for other tumour types have been tested in RCC, such as Roche/Genentech's Tarceva (erlotinib) and GSK's Tykerb (lapatinib). While results have so far been disappointing, EGFR-targeted drugs still feature amongst therapies in clinical trials in RCC.

It may, however, be more useful to downregulate HIF than to inhibit its numerous downstream targets like VEGF and TGF-α, says Dr Kaelin. As a transcription factor, HIF itself is difficult to target with a normal small-molecule drug, although Santaris Pharma and Enzon Pharmaceuticals are testing their

antisense drug candidate SPC2968 in a Phase II trial in RCC.

There are other approaches to downregulate HIF than to directly target it, says Dr Kaelin, including targeting mTOR. Both Torisel and Afinitor target one of two mTOR complexes, mTORC1. However, it is the second complex, mTORC2, which may be more important to target in RCC, he says. Drugs targeting mTORC2 are in Phase I clinical trials in advanced solid tumours, including Novartis's BEZ235 and Exelixis's XL765.

mTOR is also a key component of the PI3K-AKT pathway, and drugs inhibiting PI3K and AKT are also in development for RCC. These may also downregulate HIF, but have some advantages over the TORC1 inhibitors whose efficacy may be reduced as they may activate a negative feedback loop that exists in the pathway, says Dr Kaelin. AEterna Zentaris/Keryx Biopharmaceuticals' AKT inhibitor perifosine and Rexahn's antisense AKT-1 inhibitor Archexin are both in Phase II trials. Meanwhile, XL765 and BEZ235 also inhibit PI3K in addition to mTOR.

Besides combing the genome for frequent mutations or abnormalities in RCC as in the Cancer Genome Project, new targets may be uncovered through a "synthetic lethality" approach. Dr Kaelin's lab is attempting to discover protein kinase targets that are necessary for the survival of cells lacking functional VHL (the tumour cells), but not normal cells. A proof-of-concept study found that certain well-known oncogenes in cancer, such as MEK1 and cMET, were necessary for the survival of cells which lacked functional VHL, so that inhibitors of these would be expected to lead to the selective death of the tumour cells in RCC.

Inhibitors of the cMET/MET receptor are already in clinical trials in RCC. This is partly because the gene, which is thought to be involved in many cancer processes such as cell proliferation and metastasis, is commonly mutated in hereditary papillary RCC, and may be upregulated as well in sporadic papillary RCC. Papillary RCC accounts for about 10% of cases of RCC, and usually has a much better prognosis than clear-cell RCC. MET also may be involved in clear-cell disease; there is evidence of correlation between inactivation of VHL and increased MET signalling.

Exelixis/GSK's XL-880/GSK089, in Phase II development in papillary RCC, inhibits both MET and VEGFR2, while Amgen's AMG-102, in a Phase II trial in RCC, is an antibody targeting MET.

biomarkers

So far, it has been difficult to select optimal targeted therapies (to personalise treatment) for RCC patients except by their tumour grade and stage. There is no biomarker, such as a gene or protein, that reliably predicts response to a certain drug, in the way that overexpression of the HER2 protein predicts response to Herceptin in the approximately 20% of breast cancer patients who have this.

"We are still using targeted therapies in RCC in an untargeted manner. Drug development remains deficient in guiding patient selection based on molecular biomarkers, and tailoring therapy for those most likely to benefit from these new therapies," says Dr Lara.

Preliminary work has been done to identify predictive biomarkers for the approved drugs in RCC, with limited success with obvious candidates such as levels of VEGF in the blood or mutational status of the VHL gene.

However, a study recently published in *Cancer Cell* by John Gordon and colleagues which looked at both VHL gene status and expression of HIF protein suggested that there could be two types of clear-cell RCC that may be treated differently. In the study, tumours with wild-type (non-mutated) VHL, as well as tumours with loss of VHL that expressed both HIF-1α and HIF-2α proteins, experienced enhanced activation of the AKT/mTOR and ERK/MAPK signalling pathways. In contrast, tumours with loss of VHL that expressed only HIF-2α showed elevated c-MYC activity, resulting in enhanced proliferation.

The authors say that the first group may be more likely to respond to the newly approved RCC drugs, while the latter may be resistant. They recommend additional studies to further validate their results.

combinations

Even if multiple cell growth/proliferation, angiogenic, and other pathways are deregulated in RCC, which is very likely, it could be that hitting one crucial pathway could halt or reverse the growth of the tumour for a period of time.

"None of the pathways are sufficient by themselves to lead to the cancer – it is necessary to have all of them for the cancer to arise," says Dr Kaelin. "It therefore follows that blocking any one of the pathways might measurably impede the growth of the cancer."

Nevertheless, combinations may still be needed in RCC, as in other cancers, because it may be difficult to block a key pathway completely with one drug, or because resistance to one drug is more likely than to a combination of drugs with different mechanisms of action.

In Phase III trials in RCC are combinations of the approved VEGF/VEGFR and mTOR targeted drugs, which may affect levels of VEGF through two different mechanisms. Torisel is being tested in combination with Avastin, while Sutent is being tested in combination with Afinitor.

Combinations of the VEGF and VEGFR drugs are also being tested, including that of Sutent and Avastin. However, tolerability has been an issue in Phase I and II trials, partly because the two drugs have overlapping toxicities, so that lower doses of Sutent are being used in ongoing combination studies.

sequential therapy

Even if a crucial pathway is initially being targeted in RCC, patients will likely become resistant to their initial therapy. One reason is that within the heterogeneous mixture of tumour cells, some cells may have rare mutations that cause them to be resistant to a particular drug therapy that the bulk of the tumour is sensitive to. This subclone of cells will then become more dominant within the tumour as the others are killed by the drug.

While drugs working primarily by an anti-angiogenic mechanism of action may not be affecting the tumour cell directly, resistance to anti-angiogenic agents may be caused because of the redundancy of angiogenic stimulators. For example, after treatment with anti-VEGF or VEGFR2 drugs, upregulation of other angiogenic factors has been observed.

"The next biggest challenge in RCC is understanding the mechanisms by which these tumours become resistant to VEGF pathway agents," says Dr Stadler. "This is poorly understood but is of fundamental importance to make further advance in the disease."

Understanding mechanisms of resistance will help to determine the best sequence of drug therapies, which most likely will have to be individualised.

"My enthusiasm is less to combine these drugs," says Dr Motzer, citing the toxicity issues that have so far arisen. "The interest is now moving to sequential use of monotherapies – I think that is where the most promise currently is."

So far, one sequence of the new targeted agents has been tested and validated in a Phase III trial – VEGFR/VEGF drugs followed by an mTOR inhibitor (in this case Afinitor). Adding the median survival time seen with Sutent in its pivotal trial in the first-line setting to that seen with Afinitor in its trial results in median survival approaching three years, says Dr Figlin.

While prior failed treatment with a drug of the same class has often implied drug resistance to the class, so far it has been observed in clinical trials that previous VEGF pathway-inhibitor therapy does not predict for a negative response to a subsequent VEGF pathway inhibitor. As such, axitinib is being tested in patients who have progressed on Sutent, Avastin and other drugs.

adjuvant therapy

About 25% of RCC patients present with metastatic disease. The rest are diagnosed with localised tumours that can potentially be cured with surgery. However, either because surgery failed to remove every last tumour cell, or because there were already undetected micro-metastases present at other locations in the body at the time of surgery, about 40% of RCC patients who appeared to be cured with surgery recur and die of their disease.

Sutent and Nexavar are both being tested in trials in the adjuvant setting (including one head-to-head Phase III trial), where if they are shown to prevent tumour recurrence in a significant proportion of patients, they will be hailed as true cures for the disease. "It is possible they will work in the adjuvant setting," Dr Motzer says. "I'm hopeful – it would be a wonderful thing."

Researchers have discovered that one of the critical events required for metastasis is angiogenesis. In mice, angiogenesis inhibitors administered after the removal of localised tumours dramatically reduced the rate of metastasis.

Their effect in humans in this setting is still uncertain, however. "The mechanisms of drug action may be different in the microscopic setting where there is no angiogenesis and the macroscopic setting where the tumour already has developed blood vessels," says Dr Stadler.

Whilst the drugs' greatest value may be derived in the adjuvant setting, their side-effects are more of a concern here as some proportion of patients will have been cured with surgery alone and therefore the benefit-risk profile of the drug is different from the metastatic setting.

In the adjuvant just as in the advanced disease setting, one key is a personalised medicine approach that would ensure only those patients who need a certain treatment receive it.

Arie Belldegrun, a researcher at UCLA's Jonsson Comprehensive Cancer Center, led a study published in *Cancer* in November which distinguished three groups of RCC patients. Doctors were able to identify which patients were at a low, intermediate or high risk of recurrence. Low-risk patients had a 10-year survival rate of 92%, so could be treated with surgery alone and spared from therapy. High-risk patients had a 10-year survival of 41%, and were good candidates to receive treatment with drugs proven to reduce recurrence after surgery.

immunotherapy

The idea of inducing or reawakening the immune system to eradicate cancer remains a tantalising one. In curing a small percentage of RCC patients with metastatic disease by activating the T-cells of the immune system, high-dose IL-2 accomplished in RCC what few other drug therapies have ever done for advanced cancer patients.

The activity of interferon and IL-2 in RCC has led to its being the testing ground for more immunotherapies than most other tumour types, so that it is perhaps not too surprising that out of six therapies in Phase III trials for RCC, four are immunotherapies.

Results for each of these, which have different modes of action, have so far been inconclusive. This includes Oxford BioMedica/Sanofi-Aventis's Trovax, being tested in the advanced disease setting, and several others (Antigenics' Oncophage, Wilex's Rencarex and LipoNova's Reniale) being tested in the adjuvant setting, where some in the field believe immunotherapy will be more successful.

Nevertheless, experts express divergent opinions on the subject of immunotherapy. "During 20 years little progress has been made with immunotherapy … my excitement lies with targeted therapy," says Dr Motzer.

But Dr Bukowski counters: "I don't think we should abandon immunotherapy. We need to understand it. It should work in kidney cancer if it works in any tumour."

One of the issues with immunotherapy has been that the tumour produces immunosuppressive factors to defeat potentially effective immune responses. This may be partly overcome by administering the targeted drugs that have been shown to shrink the tumour (such as Sutent) before immunotherapy in advanced disease patients, Dr Figlin believes, and is testing such an approach in trials.

the future

The four new drugs that have improved outcomes in RCC have proven that it is not an untreatable tumour – that survival can be improved. They have also highlighted that in order to accomplish this, the underlying biology of the disease should be understood as should be the mechanisms of the drugs. There is much further to go with respect to both of these in RCC if outcomes are to improve significantly more for patients.

"One must understand the benefits and limits of what we have accomplished," says Dr Figlin.

"One can consider this a revolution" says Dr Lara. "However, it does not mean that the revolution is fully realised."

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