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Target therapy in metastatic renal cell carcinoma

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ABSTRACT

Metastatic RCC with 38,000 new cases diagnosed in the United States every year is notoriously resistant to conventional chemotherapy and is almost invariably an incurable condition. New biologic drugs are beginning to break this resistance, reflecting in the registration of four innovative agents for treatment of advanced RCC in the last 2 years, bevacizumab, sorafenib, sunitinib and temsirolimus. Small-molecule multikinase inhibitors targeting VEGF receptors (sunitinib and sorafenib) can prolong time to progression and preserve quality of life when used in newly diagnosed or previously treated patients. The anti-VEGF antibody bevacizumab enhances response rate and prolongs disease control when added to interferon. Temsirolimus, mammalian target of rapamycin inhibitor, prolongs the survival duration of patients with poor-risk disease. In this review, we report pre-clinical data, data relative to registrative phase III trials, and guideline indications for an optimal use of these new agents that are revolutionising the management of metastatic Renal Cell Carcinoma.

Metastatic RCC with 38,000 new cases diagnosed in the United States (US) every year[1] is notoriously resistant to conventional chemotherapy, and is almost invariably an incurable condition. However, new biologic drugs are beginning to break this resistance, reflecting in the registration of four innovative agents for the treatment of advanced RCC in the last 2 years, bevacizumab, sorafenib, sunitinib and temsirolimus.

1. Bevacizumab

One-half of clear-cell RCCs have upregulation of HIF-1/2 and HIF target genes including *VEGF*.[2] Bevacizumab, a humanised recombinant anti-VEGF antibody, binds all types of VEGF-A isoforms and neutralises their activities.[3] A phase III trial involving 641 patients with metastatic clear-cell RCC compared IFN combined with either bevacizumab or placebo. Bevacizumab resulted in a significantly longer progression-free survival (PFS) time (10.2 versus 5.4 months) and higher objective tumour response rate (30.6% versus 12.4%). Interim analysis showed that there was no significant survival advantage. Common toxicities seen in this trial were hypertension, proteinuria, bleeding and thrombotic events.[4]

2. Multikinase inhibitors

Small-molecule kinase inhibitors that have more than one target (multikinase inhibitors) are generating considerable excitement in the treatment of metastatic RCC. Sequencing of the human genome has identified 518 putative kinases, 90 tyrosine kinases and 58 receptor tyrosine kinases.[5] Moreover, the *in vivo* targets are likely to include kinases present in both the tumour cells and stroma (e.g. endothelial cells). Because deregulation of HIF is an important aspect of RCC development, agents that affect HIF target genes, especially those encoding VEGF and VEGF receptors (VEGFRs), may be particularly useful. Two such VEGFR inhibitors, sorafenib and sunitinib malate, demonstrated sufficient activity to receive regulatory approval for their use in mRCC in the US and Europe.

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2.1. *Sorafenib*

Sorafenib was initially found in a screen for agents to block the Raf proteins C-Raf and B-Raf. Further examination demonstrated that this compound also blocked other kinases, including VEGFR-2 and VEGFR-3, platelet-derived growth factor receptor (ΠΔGF), as well as the receptors for Flt-3 ligand and stem cell factor.[6,7]

Signalling through many receptors involves the activation of Ras, recruitment of Raf to the membrane and subsequent activation of the mitogen-activated protein kinase (MAPK)–extracellular signal–related kinase (ERK) pathway, which affects a large number of downstream cellular responses. *In vitro* sorafenib is a potent inhibitor of ERK phosphorylation in many, but not all, cancer cell lines. In particular, cell lines with activating mutations of *KRAS* appear non-responsive. However, *in vivo* growth of these resistant cell lines could still be inhibited by sorafenib, suggesting an antiangiogenic effect.[7]

The role of sorafenib in RCC was solidified in the Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET) study, in which 903 patients with cytokine-refractory metastatic clear-cell RCC of low or intermediate risk, according to the MSKCC classification,[8] were randomised to receive sorafenib or placebo. Median PFS times were 5.5 months in the sorafenib group and 2.8 months in the placebo group, and objective response rates were 10% in sorafenib arm and 2% in placebo arm. Although the difference in survival favoring sorafenib was not statistically significant, it may have been because of early crossover allowed shortly after an interim analysis showing a difference in PFS. That trial also characterised the side-effect profile of sorafenib. Discontinuation of treatment because of side-effects occurred in 10% of patients receiving sorafenib, and 13% required dose reductions for toxicity. The most important side-effects were diarrhoea, hypertension, skin rash, and hand–foot syndrome.[9] With the observed benefit of sorafenib in patients refractory to first-line therapy (mostly immunotherapy) from the TARGET trial, sorafenib was compared with IFN in untreated patients in a randomised phase II trial. Objective response rate was only 5% in patients receiving sorafenib, with no advantage over IFN in terms of response rate or PFS duration (5.7 versus 5.6 months).[10] However, from the large sorafenib open-access programme, there were 224 previously untreated patients for whom the PFS duration was 35 weeks.[11]

2.2. *Sunitinib*

Sunitinib malate is also an oral multikinase inhibitor that blocks the activity of VEGFR-2 and PDGFR, as well as Src, Abl, insulin-like growth factor receptor-1 and fibroblast growth factor receptor-1 tyrosine kinases.[12] Its effect on RCC became evident with the results of two multi-institutional phase II trials enrolling patients previously treated predominantly with immunotherapy. The first study, including 63 patients with various histologies (the large majority had clear-cell carcinoma) of RCC, demonstrated a 40% objective response rate and median time to progression (TTP) of 8.7 months.[13] The second study required prior nephrectomy and included 106 previously treated patients whose tumours were predominantly of the clear-cell type, with a response rate of 34% and median disease-free survival interval of 8.3 months.[14] Despite the broad overlap of targeted kinases between sunitinib and sorafenib, sunitinib has a distinct profile of side-effects, predominantly leukopaenia, thrombocytopaenia, stomatitis and transient skin discoloration, with skin rash and diarrhoea being less frequent. The remarkable activity of sunitinib seen in patients with refractory disease justified a large multi-institutional phase III trial randomizing 750 previously untreated patients with RCC with a clear-cell component to receive sunitinib or IFN. A higher objective response rate was seen in sunitinib arm (31% versus 6%), as were a longer PFS time (11 versus 5 months) and better quality of life. Interestingly, the benefit of sunitinib was demonstrated in all MSKCC risk groups. At last interim analysis, 13% of the patients had died in sunitinib arm versus 17% in IFN arm but this is not still significant.[15] As a result, sunitinib has emerged as the predominant first-line treatment for metastatic RCC, irrespective of risk category. Preliminary Assessment of Safety of the Expanded Access Trial showed that Response Rate and Adverse Events rate are not influenced evenly considering risk factors such as brain metastasis, non-clear-cell histology, poor PS and elder age.

With two approved multikinase inhibitors, it is important to determine the cross-resistance between these agents. So far it appears that cross-resistance is not complete and objective responses and meaningful disease stabilisation are seen when the second multikinase inhibitor (sorafenib or sunitinib) is employed. Absolute resistance to both agents is, in fact, uncommon, and was seen in only 7% of patients in one report.[16]

3. mTOR inhibitors

All mRNAs are not equally created; those with long structured 5-untranslated regions, often associated with growth and cell-cycle regulatory genes (e.g. those encoding c- Myc, cyclin D1), are poorly translated into protein unless stimulated by growth factor signalling.[17] Akt, MAPK and mTOR are critical components in this regulation. In at least one form of hereditary RCC, resulting from mutations in the TSC1/2 complex, the mTOR pathway is constitutively activated.[18] Mutations in the tumour suppressor gene phosphatase and tensin homologue deleted on chromosome ten (*PTEN*), which occur in approximately 5% of RCCs and are associated with advanced-stage aggressive disease, also activate mTOR.[19] *VHL* loss-of-function mutations lead to HIF and VEGF accumulation. In addition to proteasome-mediated destruction, HIF is also regulated at the level of protein translation initiation, which is controlled by mTOR, thus reinforcing the strong rationale for mTOR inhibitors in RCC.

3.1. *Temsirolimus*

Temsirolimus is a water-soluble ester of sirolimus amenable to i.v. infusion. Major side-effects associated with temsirolimus are rash and stomatitis.[20] In a phase II study[21], 111 patients were treated with varying doses of temsirolimus. Response rate was 7% (including one CR), median time to

tumour progression was 5.8 months and median survival time was 15 months. Interestingly, no dose–response effect was observed, and the lowest dose was chosen for a subsequent phase III trial. A large, international trial randomised 626 previously untreated RCC patients with poor prognostic features (the majority were high risk patients in the MSKCC classification) to receive treatment with IFN, temsirolimus, or the combination, which used a lower dose of temsirolimus. Although there were no significant differences in response rates (i.e. 4.8%, 8.6% and 8.1%, respectively), temsirolimus alone, but not the combination, was superior to single-agent IFN in terms of the PFS (5.5 versus 3.1 months) and overall survival (10.9 versus 7.3 months) times. Temsirolimus was also the safest of the three treatments, having the lowest rates of grade 3 and 4 toxicities.[22] That trial led to the recent approval of temsirolimus for the treatment of advanced RCC in the US Although its benefit was demonstrated in patients with poor prognostic features, its regulatory approval was not restricted to this subgroup of patients.

3.2. *Guidelines indications*

Both NCCN and EAU guidelines give an indication of sunitinib as first-line therapy of mRCC (grade of recommendation 1A). This assignment is justified for the results of the randomised phase III trial of sunitinib versus IFN. New data presented at 2007 ASCO Congress show a reduction in the risk of statistically significant progression of 47% for sunitinib arm and a PFS of 11 versus 5.1 months of interferon arm. EAU guidelines in high risk group give an indication of temsirolimus as first-line therapy (grade of recommendation 1A) by the results of the trial published in 2007. Anyway in the sunitinib randomised phase III trial, the high risk subgroup (3 or more risk factors), obtained a reduction in risk of progression of 61% versus IFN, with a median PFS of 10 versus 2 months.

According to EAU guidelines sorafenib has no indication as first-line treatment, whilst according to NCCN it can be used with a grade of recommendation 2A.

The association bevacizumab and IFN (AVOREN trial) gives a reduction in the risk of progression of 37% with a PFS of 10.2 versus 5.4 months of the interpheron arm, and a 70% of control of disease. Both EAU and NCCN guidelines do not give indication for the first-line therapy to this association with grade of recommendation 1, probably because the results of the trial did not have a critical review by a external committee, and the missed prospectic evaluation of QoL.

Conflict of interest statement

All authors disclose any financial and personal relationships with industries and organizations that can inappropriately influence this work.

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