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REVIEW

Temsirolimus: Safety and Efficacy in the Treatment of Renal Cell Carcinoma

M. Hammad Ather and Syed M. Nazim

Section of Urology, Department of Surgery, Aga Khan University, Karachi 74800, Pakistan.
Corrensponding author email: hammad.ather@aku.edu

Abstract: Surgically unresectable renal cell carcinoma (RCC) is an incurable condition. This is due to RCC's inherent chemo resistance. Cytokine therapy until recently was the mainstay of treatment. However, it showed modest response. Current advances in the understanding of the biology of RCC have resulted in the development of targeted agents. These agents include multi kinase inhibitors like Sunitinib and Sorafenib, humanized monoclonal antibody ie, Bevacizumab and Temsirolimus, a selective inhibitor of mammalian target of rapamycin (mTOR). Temsirolimus is recommended as a first line agent in poor prognosis patients with metastatic RCC. There is also emerging data on the safety and efficacy of temsirolimus in a cohort of pre-treated intermediate to poor prognosis patients with metastatic RCC. Temsirolimus has also shown better outcome over interferon α in quality-adjusted time without symptoms of progression or toxicity analysis.

Keywords: RCC, metastatic disease, mTOR, multikinase inhibitors

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Introduction

Renal cell carcinoma (RCC) accounts for 3% of all malignancies in adults and after prostate and bladder cancer is the third most frequent urological malignancy.[1] The majority of RCC is of the clear cell subtype (50%), followed by RCC not otherwise specified (26%), papillary (10%), and chromophobe subtypes (4%).[2] Although histological subtypes of RCC have been shown to differ in clinical features and genetic determinants, epidemiologic data on RCC subtypes are sparse and have not revealed consistent incidence or risk factor patterns. A meta-analysis by Lee and colleagues[3] confirms that clear cell RCC and papillary RCC are not different in survival outcomes. In addition, type 2 papillary RCC shows poorer survival than type 1 papillary RCC. Metastatic RCC has a very poor survival, with only 10% surviving for 5 years.[4] RCC is one of the most lethal genito-urinary malignancies with about 13,000 estimated cancer-related deaths in the United States in 2008[5]. It is probably one of the most lethal cancers with over 100,000 deaths globally every year.[4] It is refractory to conventional chemotherapy. Until recently cytokines interleukin II and interferon α was the mainstay of treatment. However, the response rate with these agents was low, in the range of approximately 15%.[6] Recent understanding of the biology of RCC has resulted in the development of a wide range of targeted agents. In 2007 Temsirolimus became the third drug approved for RCC after Sunitinib and Sorafenib. Temsirolimus is a mammalian target of rapamycin inhibitor which prolongs the survival in poor risk patients. It is of particular interest that RCC has been the first malignancy in which inhibition of mammalian target of rapamycin (mTOR) has proved its efficacy in a phase III trial. Such mTOR inhibitors such as everolimus and temsirolimus have shown robust clinical efficacy in treating mRCC. For example, everolimus has proved effective in patients whose disease has progressed after treatment with VEGF-targeted therapy.

The approved indication for use of temsirolimus as a first line treatment in poor prognosis patients and that of everolimus as a second line treatment in tyrosine kinase inhibitors (TKI) refractory cases is now under investigation. This addition to the existing repertoire of tyrosine kinase inhibitors has provided clinicians with newer and better therapeutic options. This hopefully will translate into a significantly improved prognosis of mRCC patients in the future. The goal of current research in this area is to find the best combination, improvement in patient benefit from existing agents and to develop newer less toxic more efficient targeted agents. Newer anti vascular endothelial growth factor (VEGF) agents such as axitinib, pazopanib and cediranib, are currently under investigation to expand the future treatment options in mRCC. Some of the recent work has focused on synergistic potential of TKIs in order to simultaneously block multiple signaling pathways. Unfortunately this approach has resulted in significant increased toxicity. Sequential TKI use has met with some success; however the optimal sequence is yet to be determined. In essence a range of potent drugs are available to patients with mRCC. However, treatment decisions have to be made carefully taking into consideration that all targeted agents are at best palliative. They are less toxic than conventional chemotherapy but they are expensive.

RCC is now known to be a heterogeneous malignancy, with several subtypes that exhibit distinct clinical and histological features. The unique molecular defects that are pathogenic for each subtype have been defined, allowing targeted molecular approaches to be developed and tested and moving RCC to the forefront of molecular therapeutics. The majority of RCC are of clear cell histological type that accounts for 75% of malignant renal tumors. Surgical resection is the effective treatment option for organ-confined disease. However, about one-third of patients either present with metastatic disease at the time of initial diagnosis or develop one after surgery, which is often refractory to cytotoxic chemotherapy.[7]

Historically, immunotherapy with either interferon-alpha (INF α) or interleukin-2 was the mainstay of treatment for metastatic renal cell carcinoma (mRCC).[8] Analysis of immunotherapy showed an overall response rate (partial or complete remission) of 12.4% only with high incidence of toxic effects.[9] And therefore, systemic treatment (chemotherapy or immunotherapy) in patients with mRCC is regarded as ineffective until the emergence of antiangiogenic drugs.[10] In a recently published review an algorithm is suggested using first and second line tyrosine kinase and mTOR inhibitor.[11] It also takes into consideration the functional and co morbid status of the patients.[11]

Targeted therapies for renal cell carcinoma

A growing understanding of the underlying molecular biology of RCC has identified several important pathways that can be targeted for molecular therapy. The high vascularity of RCC suggests that angiogenesis is fundamental to its pathogenesis. Recently, two pathways ie, VEGF and mammalian target of rapamycin (mTOR) have been identified as relevant therapeutic targeted therapies for mRCC.[12] The most important of these pathways is related to the von Hippel–Lindau (VHL) protein that regulates hypoxia inducible factors hypoxia inducible factor HIF-1and HIF-2.

VHL and HIF signaling in renal cell carcinoma

The VHL gene (tumor suppressor gene) was discovered in 1993, located at 3p25–26, and has a pivotal role in the pathogenesis of RCC and is mutated in all of patients with familial and most patients with sporadic form of clear cell RCC.[13,14] The product of the gene (pVHL) mediates the cellular responses to oxygen deprivation. Under normoxic conditions pVHL recognizes the hydroxylated HIFs and targets them for degradation.[15,16] While during hypoxia the HIFs are not hydroxylated and interaction with pVHL does not occur, leading to accumulation within the cell. HIF then translocate into the nucleus where they regulate transcription of many hypoxia-inducible genes.[16,17]

The over expression of pro-angiogenic genes leads to over expression of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) which promotes tumor angiogenesis, proliferation, and metastasis.[18]

Constitutive activation of the mammalian target of rapamycin (mTOR) also leads to increased expression of HIF; therefore, research has now focused on those agents that suppress the mTOR pathway.[19]

mTOR pathway; key steps

In the mid 1990s, studies in yeast and mammalian systems identified a 289-kDa protein with a serine/threonine kinase activity as a drug's cellular target, which was called mTOR, also named FRAP (FK506-binding protein 12 [FKBP-12]-rapamycin-associated protein).[20,21] The mTOR/FRAP gene maps to human chromosome 1p36.2.

Availability of amino acids and glucose is the key factor which regulate yeast Tor kinase activity, however its mammalian counterpart mTOR which is also expressed in human cells is regulated not only by nutrients but also by growth factors, mitogens, cellular energy and stress and controls cell growth and metabolism.[22,23]

As a key protein kinase located in cell cytoplasm, mTOR belongs to phosphoinositide-3-kinase (PI3K) proteins that controls signal transduction from various growth factors and upstream proteins to the level of mRNA translation and Ribosome biosynthesis of cell cycle regulator proteins and mediate pro-mitogenic and pro-survival signals.[24] This leads to cell cycle progression via transition from G 1—S phase and thus cellular proliferation and growth.[25]

mTOR complex

mTOR complex comprises two subunits: mTORC1 and mTORC2 and several regulator proteins. The two complexes have complementary but distinct functions.20 mTOR1 is rapamycin sensitive and mTORC2 is rapamycin insensitive and mediates stability of cellular cytoskeleton. Acting together, these complexes regulate a diverse range of processes required for basic cell growth, including protein translation, cell division, autophagy and cell survival.[23]

Effectors of mTOR

Ribosomal S6 Kinase 1 (S6K1) and Eukaryotic initiation factor 4E–binding protein 1 (4E-BP1)—both regulators of mRNA translation—are the effectors and substrates for mTORC1 complex.[26] mTORC1 acting as a PIK3 kinase causes phosphorylation and thus activation of ribosomal p70 S6 kinase (S6K) and phosphorylation/de-activation of the translational factor 4E-BP1 by releasing it from the eukaryotic initiation factor 4E (eiF4E).[27,28]

This complex eiF4E then acts as a scaffold that mediates the enzyme-substrate interactions regulating ribosome biogenesis and translation of proteins that increase cell size, proliferation and cell survival. The ribosomal protein S6 phosphorylation is an indirect measure but widely used in research as a biomarker of mTORC1 activity.[20] mTOR pathway is tightly

regulated in the normal cells however it is aberrantly activated in many tumors.

Aberrations of phosphatase and tensin homologue (PTEN)

mTOR pathway is downstream from proto-oncogene Akt/PKB. The phosphatase protein PTEN (phosphatase and tensin homologue) regulates this pathway. A suppressor gene PTEN located on chromosome 10 encodes it.[29] PTEN inhibits PI3K by selectively dephosphrylating the phosphotidylinositols and prevents Akt activation. Persistent activation of PI3K/Akt/mTOR pathway occurs as a result of mutation or loss of function of this gene leading to uncontrolled protein synthesis and proliferation.24 This occurs frequently in RCC and is a prognostic indicator of poor survival.[30]

Angiogenesis and HIF pathway

Loss of VHL function is exacerbated by the activated mTOR pathway, which further elevates HIF-1α through increased translation. Tumors with higher HIF-1a levels are more sensitive to mTOR inhibition than tumors with lower HIF-1a levels.[31]

In a xenograft model using human kidney cancer cells, loss of VHL expression with consequent elevated HIF1α levels leads to increase vascular network ie, VEGF, PDGF etc. In this model, mTOR inhibitor rapamycin inhibited the translation of HIF1α with a drop in VEGF expression and reduced angiogenesis.[25]

Unregulated angiogenesis that is a prominent feature of RCC explains the role of mTOR pathway inhibition to suppress angiogenesis. This approach differs from that of angiogenesis inhibitor Sorafenib and Sunitinib that blocks the HIF pathway distally ie, VEGF and PDGF receptors. mTOR inhibitors such as temsirolimus and everolimus act proximally by decreasing levels of HIF.[32] Thus mTOR have a direct effect on the tumor cell instead of the infrastructure.[33]

Tuberous sclerosis complex 1 and 2 aberrations

Tuberous sclerosis complex TSC1 and TSC2 proteins form a physical and functional complex in vivo, which binds and inhibits mTOR.[34] The TSC1/TSC2 complex inhibits amino acid activation of S6K1 in nutrient-deprived cells. Loss of TSC1/TSC2 results in an mTOR-dependent increase in S6K1 activity and confers resistance against amino acid starvation in nutrient-deprived cell.[35] An aberrantly high level signaling through mTOR pathway is seen in an autosomal-dominant genetic disorder tuberous sclerosis that leads to formation of hemartomas and benign tumors.[29]

Genetic alterations of mTOR pathway and tumorigenesis

Various proto-oncogenes recognized in the mTOR transduction pathway include Ras, PI3K, Akt, Rheb, S6K1, eIF4E and Cyclin D1 while tumor suppressor genes involved are PTEN, TSC1/2, LKB136, REDD1, p5337 and beclin1.[24] Mutations, amplification or persistent activation of these proto-oncogene or silencing or tumor suppressor genes lead to development of carcinogenesis.

mTOR inhibitors

Rapamycin and rapalogs

Rapamycin (Sirolimus, Rapamune) is a macrolide antibiotic originally identified as an antifungal compound in 1975 was also discovered to have immunosuppressive and anti-tumor activities.[36] Several analogs of Rapamycin also referred to, as "Rapalogs" were developed to have improved bioavailability and formulations for the treatment of cancer patients. Currently, there are more than 100 ongoing trials of mTOR inhibitors for the treatment of various advanced solid malignancies.[37]

Temsirolimus, also called as CCI-779 (cell- cycle–inhibitor 779) was the first mTOR inhibitor to demonstrate clinical benefit in patients with advanced RCC[38] and has been approved by the Food and Drug Administration of the US since 2007 for this indication.[24] Temsirolimus causes inhibition of mTOR pathway by binding to FKB-12 and thus downstream phosphorylation of 4E-BP1, allowing this protein to bind to eIF4E and thus inhibiting mRNA translation and synthesis of various proteins and growth factors.[18,39] Additionally Temsirolimus causes arrest of cell cycle at G1stage, it inhibits HIF as well.[40]

In contrast to anti-VEGFR, which is effective mainly against the conventional (clear cell) renal cell carcinoma, Temsirolimus has been shown to be effective for both clear cell and non-clear cell variants in studies. This is partly explained by the fact that in non-clear cell tumors, even in the presence of normal VHL

functions, the mTOR pathway is found to be highly activated.[41]

Clinical Studies

Temsirolimus, a derivative of sirolimus (rapamycin), inhibits mTOR, a non-RTK in the PI3K-Akt pathway controlling the translation of specific messenger RNA. This mTOR activation has multiple downstream effects, including increasing hypoxia-inducible factor 1a (HIF1A) gene expression. Furthermore, reduced phosphatase and tensin homolog (PTEN) expression has been demonstrated in some renal cell carcinoma (RCC) patients, and loss of PTEN function results in Akt phosphorylation, with downstream effects on cell growth and proliferation that may be blocked using rapamycin derivatives. This provides a strong rationale for the use of mTOR inhibitors in RCC.

Temsirolimus is a water-soluble ester of sirolimus amenable to intravenous infusion. When administered on a weekly schedule, the plasma concentration of temsirolimus decreases to sub nanomolar levels within 3 to 4 days, whereas sirolimus, the primary metabolite of temsirolimus (derived from the hydrolysis in the body of the 3-hydroxy-2-[hydroxymethyl]-2-methylpropanoic group), remains at therapeutic levels, which likely accounts for some, if not all, of the anti tumor activity.[42] Therefore, clinically relevant pharmacokinetic exposure to intravenous temsirolimus is considered to be a composite of both temsirolimus and sirolimus. Temsirolimus and sirolimus are both metabolized in the liver and are extensively excreted in feces. Patients with RCC may require hemodialysis after surgery and while undergoing chemotherapy. In a phase I trial Raymond et al[43] enrolled 24 patients with solid tumors (mostly renal and colorectal cancer). No immunosuppressive effects or opportunistic infections were detected, and the main dose-limiting toxicity was grade 3–4 thrombocytopenia. The most frequent adverse events were stomatitis and skin toxicity, as a maculo papular rash predominantly observed in head and neck. Confirmed partial responses (PR) were observed in 2 patients, 1 with RCC and the other with breast carcinoma. Thus, this study assessed the safety and preliminary activity of CCI-779 administered weekly in doses ranging 7.5 to 220 mg/m^2. In another phase I trial, Hidalgo colleagues[44] treated a total of 63 patients on a different schedule, administering CCI-779 in daily doses for 5 consecutive days every 2 weeks (0.75 to 24 mg/m^2). RCC (16 patients), colorectal cancer (10 patients), and non-small-cell lung cancer (9 patients) were the most represented tumor types. In this study, heavily pretreated patients did not tolerate doses above 15 mg/m^2/d, and this was established as MTD (maximum tolerated dose). The most frequent adverse events were mucositis, skin toxicity, and asthenia, but these toxicities were not clearly related to the dose level of CCI-779. One patient with non-small-cell lung cancer had a confirmed PR, and another 2 patients with RCC and 1 patient with soft-tissue sarcoma showed unconfirmed PR, lasting from 1 to 5 months.

In a randomized phase II trial, Atkins and colleagues[45] randomly assigned 111 patients to receive 25, 75, or 250 mg of temsirolimus as a weekly intravenous infusion. Most of the patients had received previous therapy, and response rate was 7%, with 51% of the patients being stable or better after 24 weeks. The most frequent grade 3 or 4 toxicities were hyperglycemia (17%), hypophosphatemia (13%), anemia (9%), and hypertriglyceridaemia (6%).

Temsirolimus got an FDA-approval in 2007. In a recently reported phase III trial[46] Hudes and colleague included 626 previously untreated patients with poor prognostic criteria who were randomized to one of three arms: weekly temsirolimus 25 mg intravenous, INFα 18 MIU 3 times weekly, or temsirolimus plus INFα 3 times weekly. Temsirolimus monotherapy demonstrated significantly longer OS than did the other arms of treatment (median OS was 10.9 months in temsirolimus arm, 7.3 and 8.4 months in INFα alone and in the combination arm, respectively). They concluded that temsirolimus should be considered a first-line standard of care for patients affected by mRCC with poor prognostic criteria. Recently everolimus (RAD001), another mTOR inhibitor, has been reported to improve the PFS of patients with mRCC who progressed on Sunitinib or Sorafenib or both.[47] In a phase III study 410 patients were randomized to daily oral everolimus 10 mg or placebo and were stratified by previous anticancer therapy and MSKCC prognostic score. The PFS (primary endpoint) was 4 and 1.9 months ($P < 0.001$) for everolimus and the placebo group, respectively, and benefit was seen in all 3 MSKCC risk groups. At the time of the analysis, there was no significant difference in OS; median OS was 8.8 months for the placebo group while it was not

reached for everolimus group. In the everolimus arm, the most commonly reported adverse events were stomatitis (40%), rash (25%), fatigue (20%), diarrhea (17%), and pneumonitis (8%). Based on these data, everolimus emerges as an acceptable therapy in patients with mRCC refractory to TKI treatment.

The current recommendation for use of Temsirolimus is as a first line agent little is known concerning its efficacy in VEGF refractory metastatic RCC. MacKenzie and colleagues[48] in a retrospective review reported use of Temsirolimus in VEGF refractory patients. They noted that in intermediate to poor prognosis patients with mRCC weekly intravenous administration of Temsirolimus is associated with predictable but manageable toxicity and a time to progression approaching 4 months.

In poor-prognosis patients, in the first-line setting, temsirolimus is associated with a longer overall survival and progression-free survival than interferon.[46] There is lack of conclusive data on the use and efficacy of temsirolimus in the second-line. Bojanapally et al[49] have presented their experience with compassionate versus commercial use of temsirolimus in patients who had received prior systemic therapy. The median survival was between 2.5 and 4 months, and patients who had received fewer prior therapies had longer survival.

Despite the initial success of temsirolimus, drug resistance continues to be a major obstacle. In a recent work reported by Mahalingam et al,[50] noted that the histone deacetylase (HDAC) inhibitor vorinostat enhanced the anticancer activity of temsirolimus in multiple RCC models. The anti-neoplastic mechanism of this combination appears to be multifaceted. Combination treatment led to a strong reduction in surviving levels, which was associated with the induction of apoptosis and a reduction in tumor proliferation. In addition, the combination led to enhanced disruption of angiogenesis compared to either single agent treatment. These data demonstrate that the temsirolimus/vorinostat combination has significant activity in RCC and targeted disruption of survivin levels may help sensitize tumors to mTOR or HDAC inhibitor mediated cell death.

Everolimus

Currently Temsirolimus is the only targeted agent to demonstrate a significant improvement in the primary end point of overall survival and is recommended instead of Sunitinib as a first-line therapy for poor-prognosis patients. The orally administered mTOR inhibitor everolimus has shown promising anti tumor activity in vivo and anti proliferative activity against tumor cells in vitro.[51] Due to its distinct effect on mTOR inhibition everolimus has the potential for use of mTOR inhibitors as second-line treatments.[51] Everolimus has been used in various settings including treatment naïve RCC, as second line treatment and in metastatic RCC. In a phase 2 trial, Amato and colleagues using everolimus demonstrated promising anti tumor activity in patients with mRCC, including those pretreated with cytokines.[52] In addition significant anti tumor activity is also demonstrated in patients with mRCC previously treated with multikinase inhibitors (Sorafenib or Sunitinib).[53] In a large phase 3 trial labeled as RECORD-1 patients with mRCC refractory to VEGF targeted therapies were randomized in a double blind placebo controlled multi centre trial.[54] Patients who progressed on placebo as determined by investigator assessment were allowed to cross over to receive open-label everolimus. Significantly favorable median PFS was observed in patients receiving everolimus compared with placebo second interim analysis [n = 410]: 4.0 months versus 1.9 months ($P < 0.0001$); end of double-blind analysis [n = 416]: 4.90 months versus 1.87 months, ($P < 0.001$).[55] At the end of double-blind analysis, median OS was 14.78 months in the everolimus group and 14.39 months in the placebo group.[56] No significant difference between the groups in terms of OS hazard ratio, 0.87; $P = 0.177$ was observed, although this was probably because of confounding of the end point by crossover: 81% of placebo recipients who progressed as determined by investigator assessment crossed over to open-label everolimus; 76% of the patients who crossed over had progressed within 8 wk of enrolment.[54] The median time to decline of Karnofsky performance status and Functional Assessment of Cancer Therapy Kidney Symptom Index Disease-Related Symptoms risk score was prolonged with everolimus compared with placebo (5.78 months vs. 3.84 mo, $P = 0.004$, and 4.76 months versus 3.84 mo, $P = 0.053$, respectively).[56] In addition, everolimus showed a relatively favorable safety profile. At the end of double-blind analysis, the most frequently occurring adverse events, mostly grade 1 or 2 in severity, were

stomatitis (40% of patients receiving everolimus vs. 8% of patients receiving placebo), rash (25% vs. 4%), fatigue (20% vs. 16%) or asthenia (18% vs. 8%), and diarrhea (17% vs. 3%).[54] Other treatment related adverse events included infections (10% vs. 2%) and noninfectious pneumonitis (8% vs. 0%). Laboratory abnormalities including hypercholesterolemia (76% vs. 32%), hyperglyceridemia (71% vs. 30%), and hyperglycemia (50% vs. 23%) were noted. Everolimus is the first and only agent to demonstrate significant clinical benefit in patients with m*RCC* after failure of a VEGF-targeted therapy.

Side Effect Profile of Temsirolimus

Although the targeted agents used in the treatment of RCC are reasonably well tolerated, their toxicity on a long-term basis is unknown. The wide range of targets for some of these agents inhibit can result in a wide range of side effects. The primary target of these novel agents is inhibition of angiogenesis. This is achieved via direct or indirect target of the VEGF pathway, their individual mechanisms of action are key to defining their side-effect profiles. Direct VEGF inhibition with the anti-VEGF monoclonal antibody Bevacizumab is primarily associated with side effects related to the precise inhibition of VEGF, such as proteinuria, hypertension and minor bleeding events. In contrast, non-VEGF-related side effects are observed with agents inhibiting multiple receptor tyrosine kinases and mammalian target of rapamycin inhibitors: these include diarrhea, skin rash, stomatitis, hand-foot skin reaction, hypothyroidism, and hematological and metabolic abnormalities.

Various toxicities have been noted including bone marrow and skin involvement. Easy fatigability is seen in almost all targeted agents. It is managed by first eliminating other causes like anemia and hypothyroidism. Purely drug related fatigue is treated by either dose reduction of skipping dose, in addition to providing best supportive care. Mucositis is also a frequently noted bothersome symptom following Temsirolimus administration. Low-grade mucositis is seen in up to half of the patients; however, higher grade is fortunately less commonly seen. If mucositis is not associated with concomitant fungal infection, using bland diet, adding coating agents or using topical anesthetic like Lidocaine 4% best manages it. If associated with oral candidasis adding fluconazole 200 mg BID for up to 2 weeks is recommended. Up to a quarter of patients can complain of dyspnea, higher grade is fortunately seen in less than 10%. Interstitial pneumonitis is a serious cause of temsirolimus induced dyspnea. It is important that any patient receiving this agent and complaining of dyspnea should have chest x-ray as they may require steroids. Temsirolimus induced Neutropenia is seen in 1 in 10 patients. In case of febrile Neutropenia it is important to repeat blood counts daily. Patients should be counseled to prevent infections. Often in such situation treatment interruption becomes necessary. Thrombocytopenia grade 3 is seen in about 1% patients and this may require supportive care and in some situation dose reduction or interruption. Hyperglycemia is very frequently seen with temsirolimus and can involve up to half of the patients. It is frequently managed by dietary modifications alone; however less frequently drug management may also be needed. It is important for uro-oncologists to evaluate the risk–benefit ratio for patients with metastatic disease.

Conclusions

In the recent years due to considerable advances in understanding the biology of mRCC, several new drugs have been developed. These include VEGF ligand-binding monoclonal antibody Bevacizumab, multi targeted receptor tyrosine kinase inhibitors Sorafenib and Sunitinib, the mTOR kinase inhibitors temsirolimus and everolimus, and several new agents and novel drug combinations are also being tested. Temsirolimus, an ester of rapamycin, selectively inhibits mTOR and as a consequence blocks the translation of cell cycle regulatory proteins and prevents over expression of angiogenic growth factors. They have opened new horizons in the management of mRCC. A treatment algorithm based on the best available evidence so far can be therefore postulated, though it continues to evolve as data from ongoing trials become available. The optimal sequence of therapy may be influenced by numerous factors such as MSKCC risk score and tolerability of therapy; biomarkers, such as VEGF levels, could be useful in predicting clinical benefit to therapy. Besides prior treatment status, histological sub type is also important. The use of various clinical features allows a rational use of treatment selection. An important consideration is the cost effectiveness ratios of these

agents. Norum et al[57] calculated that the cost of per life year gained in the range of €22,648 to €20,392. This has particular significance in the current difficult financial situation. In another work reported recently Thompson Coon et al[58] performed a systematic review and economic evaluation of various targeted agents in the treatment of RCC. They noted that though temsirolimus, in patients with three of six risk factors for poor prognosis, had clinically relevant advantages over treatment with IFN, and Sorafenib was superior to best supportive care as second-line therapy, that estimates from the PenTAG model suggested that none of the interventions would be considered cost-effective at a willingness-to-pay threshold of £30,000 per QALY.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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