Molecular targeted therapies for renal cell carcinoma

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New advances in technology to directly target specific molecular events in the proliferation of cancer have led to promising results in renal cell carcinoma. Response rates in excess of 70% and complete responses in advanced (metastatic) renal cell carcinoma have caused a change in the paradigm of treatment from immunotherapy. Toxicities are significant, but manageable and pushing the toxicity to tolerability may increase the response rate.

Key Words: renal cell carcinoma, metastatic, therapy, molecular

Introduction

Renal cell carcinoma is the sixth leading cause of cancer deaths in the United States.[1] In the past year, there were 189000 new cases in the world and over 93000 deaths. Most cases are diagnosed after the fourth decade of life and it is twice as common in men than women.

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At the time of diagnosis, the most common sites of metastases are the lungs (50%), bones (30%-40%), lymph nodes (30%-40%), liver (30%-40%), and the brain (5%). The hallmark of renal cell carcinoma is that it is well known to metastasize to many unusual sites including the pericardium, skin, and testicle. The tumor also has a tendency to have delayed recurrences after 5 years or more.

The mortality from renal cell carcinoma has been in large part due to the lack of any effective modality other than surgery for localized disease. Most chemotherapy has had only anecdotal success at best.

From the early 1980's, immunotherapy emerged as the treatment of choice for advanced renal cell carcinoma. Initial reports with interferon and later IL-2 showed modest (5%-25%) response rates, and the median survival was still less than 3 years.[2-4] Responses are most common in the lungs with significantly lower responses in the liver, lymph nodes, primary kidney, and bone. The best results with IL-2 have only 5% complete responders. A testimony to the ineffectiveness of systemic therapy in renal cell carcinoma is that Robson in 1969 showed an 11% 5-year survival, while 30 years later Javidan showed that the 5-year survival was only 20% despite the advances in immunotherapy.[5,6]

In the past 2 years, attention has been focused on the therapy targeted to the genetic mutations of renal cell carcinoma. Linehan et al discovered the VHL mutations associated with renal cell carcinoma which were expressed not only in von Hippel-Lindau, but also in familial and wild type renal cell carcinoma.[7] When this gene is inactivated by deletion or mutation, there follows a deregulation of Vascular Endothelial Growth Factor (VEGF) and Platelet Derived Growth Factor (PDGF).[8,9] VEGF causes increased angiogenesis, while PDGF is expressed on pericytes that form the structural support of the newly formed vessels.[10] Transforming Growth Factor alpha (TGF-α) is also regulated by the VHL gene. TGF-α stimulates autocrine growth in the proximal tubule by acting as a ligand for Epidermal Growth Factor Receptor (EGFR). EGFR and its relatives are glycoproteins with an extracellular ligand binding domain and an intracellular tyrosine kinase domain. All tyrosine receptors are inactive until they are stimulated by a ligand which changes them from a monomer to a dimer configuration. Ligands for EGFR, for example, include EGF and TGF-α.

Tyrosine kinase inhibitors are small molecular weight proteins that compete with ATP for binding in the catalytic tyrosine kinase domain which is a component of the receptors for growth factors such as EGF and VEGF. Since these bind to receptors that are frequently expressed in tumors, the hope would be that they would be preferentially effective on tumors with little side effects.

Multikinase inhibitors

Sorafenib

Sorafenib (NEXAVAR) is a tyrosine kinase inhibitor that actually has a dual action. In addition to inhibiting VEGFR-2 and PDGF-α, which are important in vasculogenesis, sorafenib also inhibits RAF-1 which is a key enzyme in the signaling pathway for cellular proliferation (a direct anti tumor effect). Initial work was reported in a phase II discontinuation trial in colon cancer. This involved a 12-week run in of sorafenib followed by a randomization pending the responses of the first 12 weeks. Patients who initially had a > 25% shrinkage of the tumor remained on the drug while patients who had a > 25% growth of the tumor in the first 12 weeks were discontinued. Those patients who were stable (± 25%) were randomized to either placebo or continuation of the drug for an additional 24 weeks. The primary goal of the study was to look at patients with metastatic colon cancer, but secondary goals of the study were to look at other refractory solid tumors. All patients had ECOG performance statuses of 0 or 1 and all had measurable disease. Sixty-five patients with renal cell carcinoma were included in the trial (33 randomized to placebo and 32 to sorafenib). There were no significant variances between the groups in histologic subtype, MSKCC risk category, or prior therapy. At the end of the 24-week trial, there were 16 (50%) of patients in the sorafenib arm that maintained stable disease, while only 6 (18%) of the placebo arm maintained stable disease ($p = 0.0077$). The progression free survival in the sorafenib arm was 24 weeks, while the placebo arm was 6 weeks ($p = 0.0087$). In the whole study, 48% experienced grade _ toxicity of some type, with the most common being hypertension (24%) and dermatologic (15%).

The initial phase III trial in renal cell carcinoma was the TARGETS trial which compared the overall survival of patients treated with sorafenib to placebo. Eight hundred eighty four patients with clear cell histology, ECOG performance status of 0 or 1, and having failed at least one systemic therapy in the past 8 months were entered into a 1:1 randomization trial evaluating 400 mg sorafenib versus placebo. There were no significant differences in age, gender, ECOG performance status, number or site of metatastases, type of prior therapy, MSKCC risk category, or prior nephrectomy. Seventy eight percent of the sorafenib arm and 20% of the placebo arm achieved some degree of reduction of the measurable tumor. Median performance free survival for the sorafenib patients was 24 weeks versus 12 weeks for the placebo arm (hazard ratio = 0.44, $p < 0.000001$). In every category (age, ECOG performance, etc), sorafenib showed a benefit in survival. See Figure 1. Toxicities in the sorafenib arm were predominantly fatigue (18%), diarrhea (30%), and dermatologic (23%-31%). Due to the magnitude of the progression free survival effect in the sorafenib arm, the study was eventually modified to allow crossover from placebo to the sorafenib arm, though investigators remained blinded.[11]

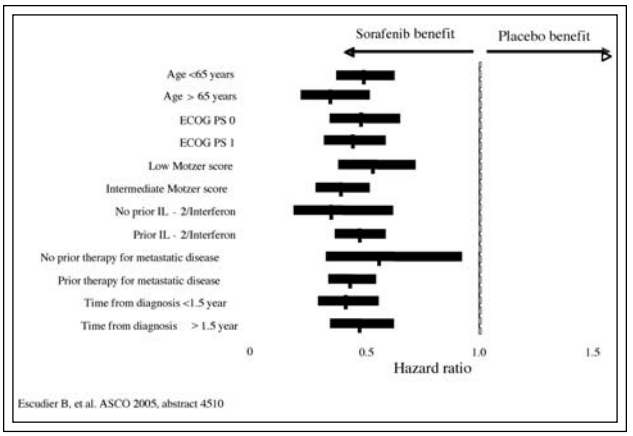

Figure 1. TARGETS trial. Progression-free survival in patient subgroups. Escudier B et al. ASCO 2005; abstract 4510.

Sorafenib was released for clinical use in December 2005 and we have used it since October 2005 initially on an investigator's trial. Our dosing schedule has been 400 mg bid 5 days on and 2 days off. Fifteen patients have been treated for metastatic renal cell carcinoma including lung, liver, nodes, bone, and pancreas. There has been no attempt to exclude patients according to histology, though the majority have been clear cell histology. Toxicities have been severe with all but one patient having at least one dose reduction for grade 3 toxicity (50% reduction). Predominant toxicities have been cutaneous including hand foot syndrome, rash, and alopecia involving all but two patients. Fatigue also had been a significant toxicity resulting in dose reduction in two patients. As patients continue to take the sorafenib, diarrhea becomes the predominant toxicity and has resulted in nearly half of the patients eventually discontinuing the medication. Currently we have two patients who had pulmonary lesions that are free of disease and off medication at 8 and 12 months from initial treatment. A third patient is currently on treatment and is NED from a metastasis to the pancreas. Four patients have had a PR and later progressed. These results exceed the reported incidence of responses, but our toxicities also exceed the reported experience suggesting that maximizing dosing to toxicity may have improve response.

Managing toxicities is clearly important in treating these patients. Hand foot syndrome is usually managed with topical agents such as Bag Balm. Generally, with time the dermatologic toxicity improves as the patient continues the treatment. Reducing or stopping sorafenib is another strategy for dermatologic toxicities, and it has been noted that when a dose reduction(s) occur, that the dose can be reescalated in time as the patient seems to develop a tolerance. Thirteen of the 14 patients who underwent dose reduction in our series were later able to reescalate their dose at least one step. GI toxicities are usually manifested as diarrhea which worsens with time. Endoscopy in these patients has shown ulceration of the colon and management includes loperamide or diphenoxylate/atropine, cholestyramine, dietary changes, or dose reduction. Grade 3 laboratory toxicities have been uncommon.

Sunitinib

Sunitinib (SUTENT) inhibits VEGFR-2 and PDGF-α, as well as other tyrosine kinases such as the type III receptor tyrosine kinase KIT encoded by the proto-oncogene c-KIT and FLT-3, a kinase expressed in the brain, placenta, primitive hematopoetic cells and found to be mutated in 30% of certain leukemias. There have been two sequentially administered single arm phase II multicenter trials reported looking at response rate, time to progression, and safety.[12,13] The first trial involved 63 patients with any renal cell histology and the second involved 106 with clear cell only. Both trials used patients who were cytokine failures and the second trial required radiographic documentation of progression and a prior nephrectomy. Patients were given 50 mg per day oral doses in repeated cycles of 4 weeks on and 2 weeks off. Dose reductions of 37.5 mg and 25 mg were allowed for grade 3/4 toxicity. Response was assessed every 1-2 cycles using the RECIST criteria. Treatments were continued until either progression of disease or inability to tolerate treatment. Overall response rates of 40% and 39% were seen in trials 1 and 2 respectively. All responses were deemed partial except 1 CR in trial 2. An additional 28% and 23% of patients achieved stable disease for ≥ 3 months. Median time to progression in trial 1 was 8.7 months. Grade 3 toxicity was observed predominantly as fatigue, GI, or dermatologic.

A phase III randomized study of 750 patients with metastatic renal cell carcinoma (clear cell histology) was carried out to compare the efficacy and safety of sunitinib versus α-interferon.[13] Patients were stratified into one of three MSKCC prognostic risk categories (favorable, intermediate, and poor). They were then randomized 1:1 to receive either sunitinib 50 mg once/day on a 4 week on/2 week off schedule (375 patients) or subcutaneous α-interferon 9 MU 3 times/week. The primary efficacy end point was progression-free survival with secondary end points as response rate (as measured by RECIST), overall survival, safety, and patient-reported outcomes (as measured by FACT-G and FACT-FKSI questionnaires). Median progression-free survival was 11 months in the sunitinib group versus 5 months in the interferon

alfa group (hazard ratio: 0.42, $p < 0.001$). Objective response rate was significantly higher in the sunitinib-treated patients than in the interferon alfa–treated patients (31%-37% versus 6%-9%, $p < 0.001$). Length of progression free survival was also longer in the sunitinib arm versus α-interferon when stratified for risk (favorable (not reached versus 8 months), intermediate (11 months versus 4) and poor risk (4 versus 1 month)groups).

Future role of multikinase inhibitors in renal cell carcinoma

Multikinase inhibitors are beginning to become the standard of care for metastatic renal cell carcinoma. There is a growing consensus that these compounds will replace cytokines as the first line treatment of patients with advanced disease. A recent case report shows that the two currently available multikinase inhibitors may be complementary with sunitinib being effective in patients who have progressed on sorafenib.[14] We currently have one patient who has progressed on sorafenib and is now responding to sunitinib. All three patients that we have switched report that their diarrhea is significantly better.

While these agents offer hope for treatment, there are caveats. One concern is that patients on multikinase inhibitors will not heal due to lack of angiogenesis, which may be problematic in patients who are having nephrectomies or other surgery after initiation of treatment with a multikinase inhibitor. There is currently no reported literature evaluating wound healing in patients on multikinase inhibitors. The second caveat is that while these drugs can be administered in a clinical setting by urologists, the toxicities can be severe and therefore these patients may be best managed by clinicians who have expertise in managing chemotherapeutic toxicities.

mTOR inhibitors

Temsirolimus

Temsirolimus (TORISEL) is a specific inhibitor of mTOR kinase, a key component of intracellular signaling involved in cell proliferation which in turn inhibits the translation of key proteins (cyclin D1, c-myc) involved in cell cycle progression (G1 growth arrest) and angiogenesis (HIF 1-alpha, HIF 2-alpha). This disruption of the signaling results in suppression of proteins that are involved in angiogenesis, making this a possible useful agent in renal cell carcinoma. Torisel was released for clinical use in May 2007 and is administered intravenously once a week (25 mg).

A three arm (1:1:1) open label clinical trial comparing temsirolimus 25 mg to α-interferon 3-18MU to temsirolimus 15 mg plus α-interferon 3-6MU was performed with a total of 626 patients with poor risk untreated metastatic renal cell carcinoma.[15] Histology was both clear cell and non clear cell renal cell carcinoma. The objectives were to compare overall survival, progression-free survival, objective response rate, and safety. All patients fulfilled at least 3/6 requirements for poor risk (LDH > 1.5 x upper limit of normal, low hemoglobin, corrected calcium > 10 mg/dl, time from diagnosis to first treatment < 1 year, performance status 60-70, or multiple sites of metastasis).

The patients in the temsirolimus arm received a median of 17 weeks of therapy while the interferon patients received a median of 8 weeks of treatment. Analysis of the data showed patients in the temsirolimus and TEMSR+IFN arms exhibited improved progression-free survival compared with the interferon arm with a median time to progression of 3.7 months versus 1.9 months ($p = 0.0001$). While temsirolimus showed an improvement in overall survival as monotherapy compared to interferon, there was no significant difference between the combination arm and interferon. Predominant grade 3 toxicities were asthenia (12%) and only 23% of patients on temsirolimus required any dose reduction.

Ligand binding agents

Bevacizumab

Bevacizumab (AVASTIN) is a monoclonal antibody directed against VEGF which binds and neutralizes the protein. It was approved by the FDA in 2004 for the treatment of carcinoma of the colon. It is generally administered on 14-day cycle intravenously. Due to its anti-VEGF activity, it has been investigated in a variety of clinical settings including renal cell carcinoma. In a phase II trial treating of 116 patients with refractory, metastatic renal cell carcinoma (histologically clear cell), patients were randomized to receive placebo, low-dose (3 mg/kg) bevacizumab, or high-dose (10 mg/kg) bevacizumab i.v. every 2 weeks.[16] Only the high dose bevacizumab arm showed any partial responses (4/39 or 10%). There was a significantly longer time to progression (TTP) in the high-dose bevacizumab arm than in the placebo arm (4.8 months versus 2.5 months; $p < .001$).

Toxicities were mild to moderate and reversible. The most common toxicity in the high dose arm was hypertension in 36% of patients (21% Grade 3).

The future for treatment of renal cell carcinoma

The treatment of metastatic renal cell carcinoma has dramatically changed in the past few years with promising agents targeting molecular pathways that are important to the growth and proliferation of renal cell carcinoma. The results show very promising response rates with acceptable toxicity. Most of these have been used as monotherapy and the opportunity to possibly use them sequentially or in combination is currently being investigated.

Disclosure

None □

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