

Treatment of Metastatic Renal Carcinoma in patients on Hemodialysis

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Introduction

Renal cell carcinoma (RCC, also known as hypernephroma) is a kidney cancer that originates in the lining of the proximal convoluted tubule, the very small tubes in the kidney that filter the blood and remove waste products. RCC is the most common type of kidney cancer in adults, responsible for approximately 80% of cases¹. It is also known to be the most lethal of all the genitourinary tumors. Initial treatment is most commonly a radical or partial nephrectomy and remains the mainstay of curative treatment². Where the tumor is confined to the renal parenchyma, the 5-year survival rate is 60-70%, but this is lowered considerably where metastases have spread. It is relatively resistant to radiation therapy and chemotherapy, although some cases respond to immunotherapy. Targeted cancer therapies such as sunitinib, temsirolimus, bevacizumab, interferon-alpha, and sorafenib have improved the outlook for RCC (progression-free survival), although they have not yet demonstrated improved survival.

Clinical experience on the use of Bevacizumab in patients with pre-existing renal impairment is limited to three case reports

We describe a case of a 69 years old Arab female with an initial diagnosis of a left renal cell carcinoma in 1996. She underwent a left nephrectomy without complications. Pathology was that of clear RCC. Patient was fine until 2005 when she was noted to have a right kidney mass. A second nephrectomy was performed. Pathology was again consistent with a clear cell RCC. She was started on hemodialysis three times weekly until February 2008 when a follow up CT scan revealed lung, liver and pancreatic lesions. She underwent radiation therapy (30 Gy) to the pancreatic bed; and was initially given Sorafenib for 7 weeks. Treatment was stopped due to severe hand-foot skin reactions. She was switched to Bevacizumab (7.5 mg/kg) biweekly and was given a total of 16 cycles with stable disease while maintained on hemodialysis; a repeat CT scan in March 2009 showed minimal residual lesions and treatment was stopped. Patient had stable disease until April 2010 when a CT scan revealed progression of her liver and pancreatic lesions. Bevacizumab was restarted again and up to date (May 2011) patient is maintained on biweekly Bevacizumab; a CT scan done in March 2011 showed no interval changes compared to last findings. She showed a good response to treatment and has had no side effects until March 2011 when patient decided to stop treatment; she was still followed up until February 2012

when she arrived in emergency room complaining of abdominal discomfort and pain in the epigastric area; a CT scan was done showing disease progression and she was restarted back on Avastin.

Garnier-Viougat and colleagues described a case report of 23-year-old patient with metastatic renal cell carcinoma requiring hemodialysis who received Bevacizumab 5 mg/kg every 2 weeks³. Bevacizumab serum concentrations were assessed after 6 months of treatment over a 2-week period. The half-life for Bevacizumab is 11.9 days. The authors noted Bevacizumab appeared to not be dialyzable.

Cicin and colleagues reported a case of a 38-year-old patient with locally advanced rectal cancer and severe chronic renal failure⁴. The patient received biweekly chemotherapy and Bevacizumab 5 mg/kg, and required hemodialysis only during the first cycle of treatment. A total of 8 cycles were completed and the patient achieved a partial response. Grade 3/4 toxicities were not observed. Inauen et al. described a case of a 48-year-old female with colorectal cancer and terminal renal failure requiring hemodialysis who received Bevacizumab with Cetuximab⁵. The patient had Bevacizumab 5 mg/kg every 2 weeks. The patient received concomitant high flux hemodialysis 3 times per week. Although the treatment was generally well tolerated, therapy was discontinued after 2.5 months because of disease progression. The authors concluded that standard doses of Bevacizumab were feasible in this patient who required hemodialysis.

The role Of VEGF in RCC

Bevacizumab is a humanized monoclonal antibody that inhibits vascular endothelial growth factor A (VEGF-A). VEGF-A is a chemical signal that stimulates angiogenesis in a variety of diseases, especially in cancer, retinal proliferation of diabetes in the eye. Bevacizumab was the first clinically available angiogenesis inhibitor in the United States⁶. VEGF is highly expressed in RCC, and RCC is a VEGF-driven disease early and throughout tumor development⁶⁻¹¹. The majority of clear cell RCC tumors are driven by dysfunction of the von Hippel-Lindau (VHL) gene⁷⁻⁸. Loss of VHL function causes upregulation of hypoxia inducible factor (HIF), which results in increased VEGF⁷⁻¹⁰. This dysfunction of the VHL gene is thought to be a very early event in clear cell RCC tumor development¹⁰. Due to the role of VHL gene dysfunction, VEGF is a primary disease driver in RCC⁸.

Bevacizumab binds directly to the VEGF ligand (which is expressed by both normal and tumor cells) to prevent its interaction with receptors on the surface of endothelial cells, thereby inhibiting the biologic activity of VEGF as observed in in-vitro and in-vivo assay systems 12-13

Avastin For Renal Cell Cancer

Avastin is an effective treatment for renal cell carcinoma. Avastin is an effective treatment for renal cell carcinoma. It is FDA approved for the treatment of metastatic renal cell carcinoma in combination with interferon alfa. All studies conducted have excluded patients with compromised renal or hepatic function and clinical experience of Bevacizumab in patients with pre-existing renal impairment is limited to four case reports. Patients treated with Avastin/interferon had a median progression-free survival of 10.2 months, compared with 5.4 months for those treated with interferon alone

There are no recommended dose reductions for the use of Bevacizumab in patients with renal and/or hepatic impairment. Based on treating physician judgment, Bevacizumab should be either discontinued or temporarily suspended. The safety and efficacy of Bevacizumab was only reviewed in patients with metastatic colorectal cancer, NSCLC, and metastatic breast cancer (MBC) in four Phase III trials 9-12.

Drugs used in RCC

Renal cell carcinoma (RCC) is associated with significant morbidity, mortality, and economic burden. Standard of care for advanced RCC has changed significantly with the development of novel targeting agents. Within the past 4 years, 6 agents have been added to the armamentarium for advanced RCC, leading to revised practice recommendations. It is imperative that oncologists be aware of current assessment and treatment practices to achieve optimal outcomes in individuals with advanced RCC

1. Everolimus

Everolimus is an orally administered inhibitor of the mammalian target of rapamycin (mTOR), a component of an intracellular signaling pathway that regulates cellular metabolism, growth, proliferation, and angiogenesis. Everolimus received FDA approval, specifically for treatment of patients with advanced RCC after failure of treatment with sunitinib or sorafenib. Moreover, it was given the category 1 level of recommendation by the National Comprehensive Cancer Network guidelines for second-line treatment of patients with advanced RCC after failure of tyrosine kinase inhibitor-therapy

2. Pazopanib

Patients with renal cell cancer and mild/moderate renal impairment were included in clinical studies for Pazopanib. There are no clinical or pharmacokinetic data in patients with severe renal impairment or in patients undergoing peritoneal dialysis or hemodialysis. However, renal impairment is unlikely to significantly affect the pharmacokinetics of Pazopanib since <4% of a radio labeled oral dose was recovered in the urine. In a population pharmacokinetic analysis using 408 subjects with various cancers, Creatinine clearance (30-150 mL/min) did not influence clearance of Pazopanib. Therefore, renal impairment is not expected to influence Pazopanib exposure, and dose adjustment is not necessary.

3. Interferon Alpha

Dose-limiting renal toxicities were unusual. Infrequently, severe renal toxicities, sometimes requiring renal dialysis, have been reported with alpha-interferon therapy alone or in combination with IL-2. In patients with impaired renal function, signs and symptoms of interferon toxicity should be closely monitored.

4. Sorafenib

No dose adjustment is required in patients with mild, moderate or severe renal impairment. No data is available in patients requiring dialysis

5. Temozolomide

No clinical studies were conducted with Temozolomide in patients with decreased renal function. Temozolomide has been generally well tolerated in clinical settings by patients with advanced RCC. In patients with RCC, the adverse effect profile of Temozolomide is primarily metabolic in nature, with minimal impact on QoL compared with the commonly seen side-effects with oral multikinase inhibitors. Temozolomide's high level of specificity for mTOR likely contributes to the tolerability of Temozolomide.

6. Sunitinib

No clinical studies on Sunitinib were conducted in patients with impaired renal function. Studies that were conducted excluded patients with serum Creatinine > 2.0 x ULN. Population pharmacokinetic analyses have shown that Sunitinib pharmacokinetics were unaltered in patients with calculated Creatinine clearances in the range of 42 -347 mL/min

Conclusion

The incidence and severity of proteinuria is increased in patients receiving Bevacizumab as compared to controls. Nephrotic syndrome occurred in < 1% of patients receiving Bevacizumab in clinical trials, in some instances with fatal outcome. In a published case series, kidney biopsy of six patients with proteinuria showed findings consistent with thrombotic microangiopathy. The safety of continued Bevacizumab treatment in patients with moderate to severe proteinuria has not been properly evaluated¹¹. And Bevacizumab did not appear to be dialyzable; but lack of enough published data and/or clinical trials in mRCC (mild/moderate/severe) is yet to be underway to evaluate the safety and efficacy on patients receiving Bevacizumab.

Until relatively recently, there were few treatment options for patients with renal cell carcinoma. Now four new drugs are available for renal cell carcinoma, which in addition to Avastin, include sunitinib, sorafenib and temsirolimus. It is anticipated that future studies will likely compare Avastin as single-agent, first-line therapy with these new therapies as well as in combination with these new agents¹⁴.

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