Original Article

Clinical analysis of everolimus in the treatment of metastatic renal cell carcinoma

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Background: Renal cell carcinoma (RCC) is the most common type of kidney cancer, and accounts for approximately 3% of all malignancies. Metastatic RCC (mRCC) is not sensitive to traditional radiotherapy and chemotherapy, therefore targeted therapy has become an important treatment option. In this study, the second-line targeted drug everolimus (Afinitor), a mammalian target of rapamycin (mTOR) inhibitor, was investigated for its clinical efficacy and adverse events in mRCC after failure of first-line targeted therapy, such as sorafenib, sunitinib or pazopanib.

Methods: A total of 21 patients with mRCC who had been treated with surgery or other therapies such as tyrosine kinase inhibitors (TKIs) were given oral everolimus (10 mg/day) until disease progression. Clinical efficacy was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) 2 months after therapy, including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The adverse events were observed, and timely treatment was provided.

Results: Everolimus extended progression-free survival (PFS) in mRCC patients from 4 to 8 months (median 6.3 months). There were 3 patients with PR, 12 with SD, and 6 with PD, and the disease control rate (DCR) was 15/21 (71.4%). Common adverse events included stomatitis, rash, and pneumonitis.

Conclusions: This study provides further support that everolimus is still an important option in mRCC treatment after failure of first-line targeted therapy. However, clinical studies are still needed to further improve its therapeutic efficacy.

Keywords: Everolimus; metastatic renal cell carcinoma (mRCC); mammalian target of rapamycin (mTOR); targeted therapy

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Introduction

Renal cell carcinoma (RCC), the most common type of kidney cancer, accounts for approximately 3% of adult malignancies (1). According to the European Association of Urology Guidelines on RCC [2019] (2), localized RCC can be cured with surgery including radical nephrectomy and partial nephrectomy. Unfortunately, many RCC patients are diagnosed with distant metastasis or local recurrence, and surgery is not a curative option (3). However, metastatic RCC (mRCC) is refractory to conventional chemotherapy and radiation therapy (4). At present, the

Table 1 Summary of the clinical characteristics of 21 patients with metastatic renal cell carcinoma (mRCC)

Clinical features	Number of patients
Age	
Mean	49
Range	16–69
Gender	
Male	14
Female	7
Smoking history	
Yes	9
No	12
Hypertension	
Yes	7
No	14
Diabetes mellitus	
Yes	5
No	16
Lymph node metastasis	
Yes	16
No	5
Distal metastasis	
Yes	13
No	8

existing chemotherapy research data have not shown that chemotherapy has anti-tumor effect on mRCC or can improve the survival time of patients. Radiotherapy used to be mainly used as adjuvant therapy after radical nephrectomy and palliative treatment for metastatic lesions. Most studies have failed to show that postoperative radiation therapy improves survival or reduces local recurrence. Currently, the primary objective of radiation therapy for patients with metastatic renal cancer is to alleviate the symptoms of bone metastasis. Therefore, targeted therapy is very important for mRCC (5).

Targeted therapy agents for mRCC include sorafenib, sunitinib, bevacizumab, pazopanib, and axitinib, which inhibit vascular endothelial growth factor (VEGF) and its receptor (VEGFR), and everolimus and temsirolimus, which inhibit mammalian target of rapamycin (mTOR) (6,7). Everolimus has been approved as a second-line therapy in mRCC after failure of first-line VEGFR tyrosine kinase inhibitors (TKIs) (8). Therefore, it is of great value to carry out further clinical research to improve the therapeutic efficacy of everolimus.

In this study, 21 patients with mRCC who had been treated with surgery or other therapies were then given everolimus. The results indicated that everolimus is a safe and effective treatment for mRCC.

We present the following article in accordance with the TREND reporting checklist (available at http://dx.doi.org/10.21037/apm-20-2465).

Methods

All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University (No. 2019MEC008) and informed consent was taken from all the patients.

Basic clinical characteristics of patients

A total of 21 patients were diagnosed with mRCC (lymph node metastasis or distal metastasis) in the Fourth Hospital of Hebei Medical University, and the basic information is listed in *Table 1*.

Primary therapy

Patients who met the surgical indications (17/21) were first treated with surgery (radical nephrectomy or partial nephrectomy). All 21 patients then received at least one TKI and developed drug resistance.

Everolimus therapy

All patients were given everolimus (10 mg/d) until disease progression by consulting Urologist or Oncologist. The recommended dosage of Afinitor is 10 mg orally once daily until disease progression or unacceptable toxicity (Afinitor prescribing information. Basel, Switzerland: Novartis phama AG; 2010).

Efficacy evaluation

Clinical efficacy was assessed by the Response Evaluation

Criteria in Solid Tumors (RECIST) (9). The response was divided into 4 levels: complete response (CR, disappearance of all target lesions), partial response (PR, at least a 30% decrease in the sum of diameters of target lesions), progressive disease (PD, at least a 20% increase in the sum of diameters of target lesions), and stable disease (SD, neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD).

Adverse events

Adverse events (AEs) were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE v3.0) (10).

Statistical analysis

The study was designed to assess the efficacy and safety of everolimus. A total of 21 patients were planned to be included. Data were summarized with respect to efficacy measurements and safety measurements. Data were analyzed using the SPSS 21.0 statistical software (IBM, USA). The count data are described numerically and as a percentage (%).

Results

First-line therapy of patients

The most common first-line TKI was sorafenib (12/21), and the other common TKIs included sunitinib or pazopanib. The majority of patients had received only one TKI, and the minority had received more than one.

Clinical efficacy

The duration of progression-free survival (PFS) was determined by a professional clinician according to clinical and imaging data. The median PFS was 6.3 months (4 to 8 months), which was slightly higher than previous reports (median PFS 5.1 or 5.4 months) (11,12). There were 3 patients who achieved PR, 12 achieved SD, and 6 experienced PD, and the disease control rate (DCR) was 15/21 (71.4%).

Adverse events

The incidence of AEs (any grade) was 90% (19/21) with everolimus. The most common AEs were stomatitis (16/21), rash (6/21), and pneumonitis (3/21). All these AEs were relieved after specific treatment, and did not affect further treatment with everolimus.

Discussion

Compared with other cancers, RCC is resistant to radiotherapy and chemotherapy, making adjuvant therapy after surgery challenging (13). Thus, the 5-year survival rate is less than 12% for mRCC patients (14). The management of patients with mRCC has changed dramatically since the advent of new therapeutic agents, such as sorafenib, sunitinib, everolimus, and temsirolimus (15). According to NCCN Guidelines [2019], Sunitinib, Pazopanib and Sorafenib (VEGFR-TKIs) are the first-line standard for treating mRCC patients (16,17). However, most patients eventually experience disease progression on first-line targeted therapy (18). Both everolimus and temsirolimus are serine-threonine kinase inhibitors of mTOR (19,20). They are approved for the treatment of mRCC as the mTOR signaling pathway is typically activated in most RCC (21). Everolimus is a second-line treatment option when first-line treatment fails (16,17). It plays an anti-tumor role through its inhibition of cell growth, proliferation and angiogenesis (22). In the pivotal ECORD-1 study, everolimus significantly prolonged progression-free survival (PFS) in mRCC patients whose disease had progressed on sorafenib, sunitinib (23).

Many clinical trials have verified the efficacy of everolimus in the treatment of mRCC (23,24). As everolimus has not shown therapeutic advantage over the first-line drugs such as sunitinib and sorafenib (25,26), it is used as a second-line drug. However, everolimus is generally well tolerated and provides clinical benefit for mRCC patients after first-line sunitinib or other anti-VEGF therapies (27,28). All these results demonstrate that everolimus can be used as one of the standard options in second-line therapy for patients with mRCC (29).

For patients with mRCC, sequential treatment with multiple lines of therapy may afford sustained clinical benefit (30). In recent years, with the continuous development of medical technology, immunotherapy has been recognized in the treatment of mRCC, among which immunocheckpoint inhibitors (ICIs) and tumor vaccines have been widely used in the prognosis treatment of patients with mRCC and has a good effect. Recent clinical trials have indicated that other drugs, such as nivolumab (anti-PD-1 antibody) and cabozantinib (oral, small-

molecule TKI), are better than everolimus in the treatment of mRCC (31-33). The PD-1 inhibitor nivolumab improved the OS rate of patients with mRCC following VEGF inhibitors. Based on this evidence, everolimus may become a third-line or subsequent line of treatment for mRCC (34). However, everolimus cannot lose its efficacy or have increased toxicity as a third-line drug (35). Although the average cost per life-year (LY) of everolimus was higher than nivolumab (36), the total mean cost per patient for everolimus was lower than nivolumab (37). As for the reasons, considering the accessibility, indications and medical insurance policies of drug in China, some drugs have not yet been approved by China Food and Drug Administration. From the perspective of adverse events, various immune-related adverse events caused by immunization or combined immunotherapy involve various organ systems of the whole body, which are more complex to deal with, some of which require treatment with glucocorticoids or immunosuppressants, close monitoring in hospital, which will indirectly lead to higher medical costs. Therefore, for middle-high-risk patients, combined immunotherapy is the dominant population. According to different risks of immunotherapy is gradually increased. And for low-risk patients, considering the cost-effective of comprehensive treatment, targeted drugs are still recommended as the first choice. Targeted drugs have been carried out in China for more than 10 years, with rich clinical practice, accurate efficacy, accessible drugs and are covered by national medical insurance.

In this study, we further evaluated the efficacy and safety of everolimus in patients with mRCC. Our results provide further support that everolimus is still an important option for mRCC patients after first-line sorafenib, sunitinib or pazopanib therapy. In addition, the treatment of mRCC with everolimus has standard management for AEs (38). The AEs are moderate and can be relieved with specific treatment. Stomatitis is an inflammation of the mucous membranes in the oral cavity, inner surface of the lips, or tongue. Most patients treated with everolimus will develop stomatitis within the first 2 months of treatment. In our study, the 16 everolimus-treated patients who developed stomatitis only have minimal symptoms and can have normal diet, by consulting stomatologist, we give these patients oral rinsing therapy with non-alcoholic mouth wash or 0.9% salt water, meanwhile, continue everolimus treatment and has no change in dose. The typical onset for patients experiencing pneumonitis occurs within 2–6 months of treatment initiation. Most cases of pneumonitis are manageable. In our study, 3/21 patients are asymptomatic and are only found by radiographic. By consulting pulmonologist, we have no intervention in these 3 pneumonia patients and continue Everolimus treatment and has no change in dose. After adopting the corresponding treatment of Mupirocin Ointment and the nursing countermeasure, such as wear cotton clothing and avoid scratching, the AEs of the 6 rash patients are relieved. As long as both clinicians and patients are aware of the potential AEs of everolimus, most of treatment-related AEs are manageable with pretreatment planning, careful on treatment monitoring and prompt attention when they manifest. Therefore, everolimus is still necessary for the treatment of mRCC.

This study also has some limitations, due to small numbers of enrolled patients, the absence of a control group and the descriptive nature of analyses, we should interpret the result with caution. So, further studies are needed to expand the number of patient population and improve research methods.

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Footnote

Reporting Checklist: The authors have completed the TREND reporting checklist. Available at http://dx.doi.org/10.21037/apm-20-2465

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee

of the Fourth Hospital of Hebei Medical University (No. 2019MEC008) and informed consent was taken from all the patients.

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