Evaluation of second-line and subsequent targeted therapies in metastatic renal cell cancer (mRCC) patients treated with first-line cediranib

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Abstract

Introduction: Pivotal phase III trials have positioned angiogenesis inhibitors as first-line therapy for the management of most advanced or metastatic renal cell carcinomas (mRCC). Approaches to second-line therapy, however, remain more controversial with respect to drug selection and drug sequencing.

Methods: In this study we evaluated mRCC patients who were initially treated on the first-line National Cancer Institute (NCI) trial with the highly potent vascular endothelial growth factor receptor tyrosine kinase inhibitor (TKI), cediranib, to determine the efficacy and tolerability of subsequent therapies.

Results: Twenty-eight (65.1%) of the 43 patients enrolled on the first-line cediranib trial were known to receive second-line therapy, most commonly sunitinib (n = 21), with 4 (14%), 2 (7%) and 1 (3%) patients receiving temsirolimus, sorafenib, and interleukin, respectively. Of these, 14 (50%) went on to have 3 or more lines of therapy. The progression-free survival (PFS) proportion (PFS) at 1 year from starting second line was 30% (14.5%–47.9%). Longer duration of first-line cediranib treatment was modestly associated with longer duration of second-line treatment (Spearman rho 0.26). Patients who discontinued cediranib for toxicity were less likely to receive second-line sunitinib.

Conclusion: In this real world evaluation, sequential use of TKIs for the management of mRCC was common. PFS with sequential TKIs was similar to observed and published results for any second-line therapy. Prior toxicity affected treatment patterns and the frequent use of at least 3 lines of therapy underscores the need for prospective sequencing trials in this disease.

Introduction

Renal cell cancer (RCC) is the 10th most common cancer in the United States with an estimated 63 920 150 new cases and 13 860 deaths annually.[1] The most common histology is clear cell carcinoma; once the disease is metastatic, RCC is generally incurable. Despite low response rates and poor tolerability, immunotherapy with interferon or interleukin was considered standard treatments in this disease. However newer therapeutic agents targeting the vascular endothelial growth factor receptor (VEGR) pathway (tyrosine kinase inhibitors [TKIs], such as sunitinib, sorafenib, pazopanib and bevacizumab) or the mammalian target of rapamycin (mTOR) pathway (temsirolimus, everolimus) have significantly changed the treatment landscape in metastatic RCC (mRCC). Unlike immunotherapy, these newer agents are generally better tolerated and have better antitumour efficacy. Although these treatments often prolong progression-free survival (PFS) and, in some cases, overall survival (OS), disease progression eventually occurs necessitating subsequent therapies to maintain disease control and quality of life.

The VEGFR TKI, sunitinib, became standard first-line treatment for mRCC in 2011 based on the landmark trial by Motzer and colleagues. Trial results showed improved OS (26.4 vs. 21.8 months, $p = 0.051$), PFS (11 vs. 5 months, $p < 0.001$) and response rates (47% vs. 12%, $p < 0.001$) compared to interferon.[2] More recently, another TKI, pazopanib, with a slightly different side effect profile was also approved by the FDA for first-line mRCC based on the COMPARZ trial which showed both tolerability and non-inferiority compared to sunitinib.[3] For patients progressing on a first-line TKI, everolimus is commonly used second

line based on the RECORD 3 trial that showed an OS benefit compared to placebo.[4] Another potential second-line option is the use of an alternate TKI, such as sorafenib, which showed in the INTORSECT study to have comparable efficacy to temsirolimus.[5]

At this point, it is still unclear what sequencing strategy will maximize efficacy and minimize toxicity in a given patient. Furthermore, little is known as to how factors, such as anticipated toxicities of subsequent treatments, availability of trial data and drug access, affect therapeutic choices in real world settings. In this study we evaluated mRCC patients who were initially treated on the first-line National Cancer Institute (NCI) trial with the TKI, cediranib, to determine the efficacy and tolerability of subsequent therapies.[6]

Methods

Patients eligible for the single arm NCI 7128 (NCI Contracts: N01CM17107, N01CM62203) phase II parent study reported by Sridhar and colleagues had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, adequate organ function and measurable disease.[6] Following study drug discontinuation, patients were followed and treated off trial at their respective institutions, according to institutional protocols. Patients eligible for our analysis received second-line therapies according to physician discretion and were treated until progression, toxicity, physician discretion or death. Following ethics approval, we retrospectively collected clinical outcome data from clinical research forms. Descriptive statistics were used to describe the patient baseline characteristics and antitumour efficacy. PFS and OS were calculated using the Kaplan-Meier method and calculated from the start of first-line cediranib and from the start of second-line therapy. Spearman correlation coefficients were used to evaluate the relationship between first- and second-line responses. Date of data cut off was March 1, 2013. Statistical analysis was performed using SAS software (SAS Institute, Cary, NC).

Results

In the parent single arm phase II study, mRCC patients were treated with first-line cediranib at a starting dose of 45 mg daily.[6] Patients remained on trial until progression, intolerance or removal at the physician's discretion. Forty-four patients were registered to the cediranib parent trial, 1 patient never received treatment and was excluded from analysis.

Demographics

Twenty-eight (65.1%) of the 43 patients were known to receive second-line therapy; of these patients, most were male 19 (28%). All women in the first-line study received second-line therapy as compared to only 68% of men. The average age at initial RCC diagnosis in the 28 patients receiving second-line therapy was 59 years. ECOG performance status was available at the time of initiation of second-line therapy for 27 of the 28 patients: 22 patients (82%) had an ECOG performance status of 0 or 1, and 5 patients had an ECOG performance status of 2 or worse (18.5%)

Prior treatment

For patients who went on to receive second-line treatment, median time from initial diagnosis of renal cancer to first-line cediranib was 12.3 months (range: 0.2-107) compared to 25.6 months (range: 2.3-173) for those who did not receive second line. The duration of initial cediranib treatment was similar in both groups: 8.9 months (range: 0.4-51) and 5.1 months (range: 0.8-41.7) for those who did and did not receive second-line therapy, respectively. Cediranib-related toxicity occurred in 14.3% ($p = 0.42$) of those who received second-line treatment versus 26.7% of patients who did not. Reasons for cediranib discontinuation included disease progression (78.6% vs. 46.7%), toxicity (14.3% vs. 26.7%), and study withdrawal (7.1% vs 6.7%) for those who did and did not receive second-line therapy, respectively. Patients discontinuing cediranib secondary to progression were more likely to receive sunitinib, while patients discontinuing cediranib due to toxicity were more likely to receive temsirolimus. The median duration from stopping cediranib to starting second-line therapy was 1.0 month (range: 0-11.3).

Second-line treatment

Twenty-eight (65.1%) of the 43 patients were known to receive second-line therapy mostly sunitinib (n = 21), with 4, 2 and 1 patients receiving temsirolimus, sorafenib, and interleukin, respectively. The individual reasons why patients did not receive second-line therapy were not available.

Third-line therapy

A total of 15 patients received a third-line therapy, and 4 received a fourth-line therapy. In the third-line, patients received either temsirolimus (n = 6), everolimus (n = 4), sunitinib (n = 3), sorafenib (n = 1), or interferon (n = 1). The main sequences were cediranib-TKI-TKI (n = 2), cediranib-TKI-mTOR (n = 11), cediranib-mTOR-TKI (n = 1), and cediranib-TKI-IFN (n = 1). In the fourth-line, 1 patient each received sorafenib, everolimus, an anti PD-1 antibody (on trial) and a multi-cyclin dependent kinase inhibitor (also on trial). At the time of data cut-off, 9 patients were still alive, of which 4 were still receiving active therapy, 3 were on active

surveillance, and the remaining 2 had no data regarding subsequent management.

Progression-free and overall survival

From initiation of second-line therapy (n = 28), 1 year PFS was 30.4% (range: 14.5-47.9%) and 1 year OS was 89.1% (range: 70.0%–96.4%) (Fig. 1, Fig. 2). Focusing on the patients who received second-line sunitinib (n = 21), 1 year PFS was 28.6% (95% confidence interval [CI] 11.7%–48.2%) and 1 year OS was 61.9% (95% CI 38.1%–78.8%).

Best response

Twenty patients were evaluable for best radiological response. We observed 2 (10%) patients with a partial response, 5 (25%) patients with stable disease and 13 (65%) patients with progressive disease. For those individuals with stable disease, 2 achieved stable disease for between 4 to 6 months, and 3 achieved long-term stable disease (>6 months). The median time to best response was 3 months and the median duration of second-line therapy was 4.6 months (range: 1.3–12.3). The reason for discontinuing second-line therapy was progressive disease for 15 patients (53.6%), and while 10 patients had incomplete data at the time of data cut off, only 1 patient discontinued treatment due to toxicity.

A modest association between response to first-line treatment and response to second-line treatment was noted. For the 15 patients who achieved a partial response on cediranib, 2 (13%) had a partial response, 1 (7%) had stable disease, 4 (27%) had progressive disease, 4 were inevaluable and 4 did not receive second-line treatment. For the 18 who had a best response of stable disease with cediranib, 3 (17%) had stable disease, 6 (33%) had progressive disease, 3 were inevaluable and 6 did not receive second-line treatment. For the 6 patients who experienced progressive disease with cediranib, 2 did not receive second-line treatment, 2 had progressive disease, and 2 were inevaluable – no patient with progressive disease on cediranib had a response to second-line therapy. Patients were inevaluable due to the lack of repeat imaging.

Longer duration on cediranib was only modestly associated with longer duration on second-line treatment (Spearman rho=0.26) and with improved survival (hazard ratio=0.95/month increase in duration on cediranib, 95% CI 0.90–1.01, $p = 0.077$) from the start of second-line therapy, among those receiving second-line treatment.

Discussion

In this study, we evaluated real world treatment sequences, efficacy and tolerability of physician-selected therapies in mRCC patients previously treated on the first-line trial with the potent TKI, cediranib. At the time of the initial cediranib study, there were no available data on how to sequence therapies in mRCC. Since then, 3 important trials have been reported: (1) the RECORD-1 trial (everolimus or placebo after sunitinib, sorafenib or both); (2) the AXIS trial (axitinib or sorafenib after a variety of first line therapies including

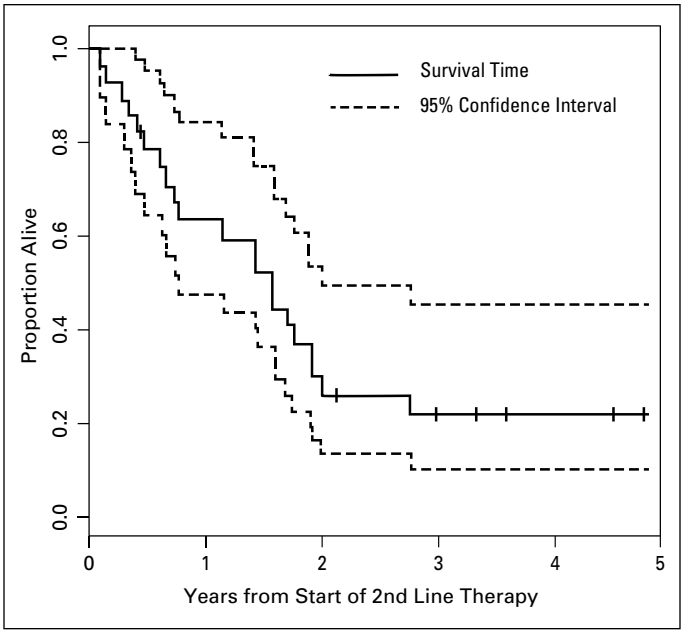

Fig. 1. Kaplan-Meier survival curves from initiation of cediranib for patients who did and did not receive second-line therapy.

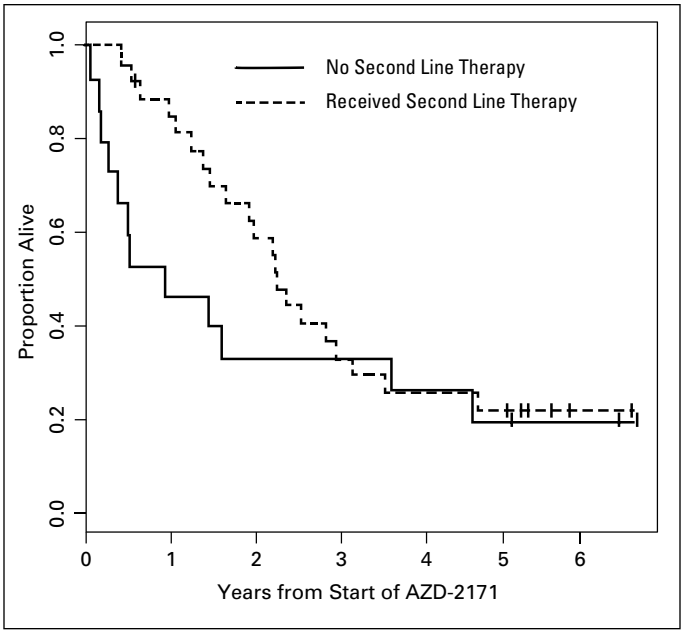

Fig. 2. Kaplan-Meier survival curves from the start of second-line therapy.

a TKI, mTOR, or immunotherapy); and (3) the INTORSECT trial (temsirolimus or sorafenib after first line sunitinib).[4,5,7] While these studies address important questions regarding the efficacy of one drug used after another in sequence, they do not provide information comparing different sequencing strategies head to head. Furthermore, it is not well-delineated how physicians currently use the multitude of mRCC targeted agents off-study, in the clinic. The patients in our analysis were those who progressed on the first-line TKI, cediranib, and received physician's choice further lines of therapy, representing a relatively unique population in which to assess current, real world uses of targeted agents in mRCC.

As expected, patients receiving second-line therapy had improved OS at 1 year compared to those who did not (89.1% vs. 74.3%, respectively). For patients receiving second-line therapy, the most commonly used agent was sunitinib. We found that PFS at 1 year for patients receiving TKI in sequence (cediranib-sunitinib) was similar to the PFS of the entire second-line cohort (28.6% vs. 30.4%). The OS at 1 year was also similar regardless of whether a TKI or alternate targeted therapy was used as second line (61.9 vs. 63.5 months, respectively). In our limited and highly selected study population, median PFS for any second-line therapy was 6.9 months; this was consistent with results from experimental treatment arms of large sequencing trials, including RECORD 1 (4.9 months), AXIS (6.7 months), and INTORSECT (4.3 months).[4,5,7]

A modest association between first-line cediranib and second-line sunitinib response was observed. According to Porta and colleagues, patients with mRCC resistant to TKI can be divided into 4 groups based on the mechanism of resistance or intolerance and this may guide further therapeutic decision-making. Acquired resistance to VEGF-inhibition usually develops within 6 to 11 months and this population with shorter responses may benefit from a switch to a target for an alternate pathway. In patients who achieve long-term disease control, continued VEGF pathway inhibition may remain an attractive option, particularly if a more potent TKI with a different side effect profile is used.[8-10]

Although over 75% of patients who received second-line therapy received a second TKI, those who experienced TKI related toxicity in the first line were unlikely to be rechallenged with a second drug of the same class. The risk of overlapping drug toxicity in sequential use of TKIs may have an important impact on decision-making. The most common grade 3/4 cediranib related toxicities on the original study were hypertension (36%), fatigue (30%), hand-foot syndrome (16%), and diarrhea (11%).[6] Of the 8 patients experiencing these effects, 4 did not receive second-line therapy, 3 received a different class of drug (temsirolimus) and only 1 received another VEGF TKI (sunitinib, but discontinued after 2.5 months due to progression). It is not well-understood if toxicities are cumulative when TKIs are used sequentially and how this might be addressed by the use of TKIs with different toxicity profiles. For example, pazopanib has lower rates of grade ≥3 cytopenias and other widely regarded class-related toxicities, such hand-foot syndrome, hypothyroidism and mucositis, are also less common.[3] Similarly, axitinib has lower rates of hand-foot syndrome.[7] Our real world data suggest that physician preference is to avoid overlapping toxicities in subsequent lines of therapy. In addition, for patients who progress on a first-line non-sunitinib TKI (such as cediranib), it is unknown whether post-sunitinib data can be extrapolated on the premise of shared drugs class.

In addition to toxicity, performance status and drug funding also play important roles in therapeutic decision-making. Sunitinib was selected as second-line treatment 75% of the time and was generally well-tolerated; disease progression, not toxicity, was the reason for treatment discontinuation. Of the 3 patients receiving temsirolimus, 2 had an ECOG performance status of 2 consistent with the first-line trial which included poor performance status patients.[11]

Drug accessibility and drug funding also play a key role in therapeutic decision-making. Most patients likely received second-line sunitinib due to its availability, while those who received temsirolimus did so likely because it was well-tolerated and had an indication for patients with poor prognosis. The decision to offer sorafenib to 2 patients and interleukin to 1 patient may have also been dictated in part by drug accessibility. Taken together, availability of data, patient performance status and drug accessibility all appear to play important roles in treatment selection in mRCC.

We found that a number of patients received at least 3 lines of therapy, highlighting the importance of head-to-head prospective sequencing trials particularly as the number of available agents in this disease increases. As in the second-line setting, drug selection may depend on the sequencing of first- and second-line agents, toxicities, functional status, clinician experience, and practical issues, such as drug availability and funding. In the AXIS trial, 95% of patients received everolimus as third-line therapy. In the RECORD-1 trial, after both a TKI and everolimus, PFS was 5.3 months for sorafenib; 8 months for sunitinib; and 12 months for the FGF inhibitor dovitinib. A small retrospective study, which evaluated 34 patients who received third-line sorafenib after first-line sunitinib and second-line everolimus or temsirolimus, showed that sorafenib was well-tolerated, and 23.5 % of patients showed a response.[12] Despite the paucity of data, it is possible that patients who retain a good performance status may still benefit from subsequent lines of therapy on a carefully considered case-by-case basis.

Several study limitations are acknowledged. This was a retrospective analysis enriched for individuals sufficiently fit to receive second-line therapy. Observed survival may

be due to treatment effect or natural history. Low numbers of patients in each treatment strategy did not allow for the assessment of statistical significance with sufficient power. In addition, we were unable to assess some factors that may have affected the likelihood of second-line TKI response.[13]

Conclusion

Sequential use of 2 TKIs with markedly different potencies, in this small, highly selected mRCC population produced similar PFS and OS outcomes to strategies where other TKI-TKI combinations or a TKI-non-TKI combination were tested. Further understanding of the molecular mechanisms underlying both response and resistance to these agents and the expansion of head to head clinical trials comparing different sequencing strategies may help to better personalize treatment decisions in mRCC. Incorporating factors, such as patient fitness, treatment tolerance, and drug funding, will also be very important.

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