Pazopanib as a possible option for the treatment of metastatic non-clear cell renal carcinoma patients: a systematic review

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Abstract

Background: Effective systemic treatment of non-clear cell renal carcinoma (nccRCC) is still an unmet clinical need, with few studies to support an evidence-based approach. To date, the only recommended standard first-line treatment is sunitinib. Pazopanib may also be used in nccRCC but its place in therapy is not clearly established. It has comparable efficacy and better tolerability than sunitinib in clear cell renal carcinoma. Our objective was to review the use of pazopanib in metastatic nccRCC.

Methods: We conducted a systematic review according to PRISMA guidelines. Any type of study reporting the use of pazopanib in metastatic renal cell carcinoma including cases with non-clear cell histology was eligible.

Results: In all, 15 studies were included in our analysis, including a total of 318 nccRCC patients treated with pazopanib. Most studies were retrospective (n=12); three were prospective trials. The specific outcomes of nccRCC patients were reported by four studies. Pazopanib alone as first-line treatment gave overall response rates ranging from 27% to 33%, disease control rates of 81–89%, median progression free survival of 8.1–16.5 months and median overall survival of 17.3–31.0 months. Grade 3–4 adverse events rates were 21–55%.

Conclusion: The present review provides for the first time a systematic summary of evidence about the possible use of pazopanib as first-line treatment for nccRCC, with a favorable outcome despite the low strength of evidence. Pazopanib could be considered as a possible therapeutic option in this setting.

Keywords: anti-VEGF, chromophobe, non-clear cell renal carcinoma, papillary, pazopanib

Introduction

Non-clear cell renal carcinoma (nccRCC) represents a pool of heterogeneous diseases, in reality no more similar to each other than to clear cell renal carcinoma (ccRCC). According to the International Society of Urologic Pathologists/World Health Organization (ISUP/WHO) 2016 classification, the term “clear cell” is reserved for the tumor diagnostic entity characterized by morphological, immunophenotypical, and molecularly distinct characteristics such as clear cell aspects, most CAIX, CD10, cathepsin-k, and PAX-8 positive for immunoexpression and affected by VHL gene mutation. The spectrum of the ccRCC “entity” shows a wide range of morphology, sometimes with the absence of clear cells, but still characterized by the driver VHL mutation. Instead, for nccRCC, the initial oncogenic event for nccRCC is not VHL-driven, and VHL mutations are less common among the classical non-clear histologies of chromophobe, collecting duct, medullary and unclassified RCC, with these classical non-clear histologies accounting for approximately 20% of all RCC cases. Along with these classical non-clear histologies, the discovery of “apparent ccRCC” with no VHL

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mutation and activation of other molecular pathways, which, irrespective of the presence of cells with clear cytoplasm, maintain VHL function and are driven by Xp11 and TFEB rearrangements (translocation MiTF family RCC) or mutations in other molecules such as in succinate dehydrogenase-deficient RCC, acquired cystic kidney disease-associated RCC, clear cell-papillary RCC, and tubulocystic RCC. Most tumors show an apparent ccRCC morphological phenotype, thus the routine use of an immunohistochemical panel is needed to rule out ccRCC versus nccRCC.

The systemic treatment of advanced or metastatic nccRCC (mRCC) is supported by very scarce evidence, composed largely of retrospective or small phase II studies and subgroup analyses of expanded access program (EAP) studies or prospective trials in patients with any RCC histologies. According to the National Comprehensive Cancer Network (NCCN) guidelines, the current recommendations for nccRCC systemic treatment are enrollment in a clinical trial or treatment with the vascular endothelial growth factor receptor (VEGFR)-inhibitor sunitinib as the preferred regimen. Indeed, sunitinib is currently the only evidence-based choice in such minor histologies, based on evidence from some published studies (including phase II trials) and from the large number of nccRCC patients treated with this drug in the EAP. Evidence from the prospective clinical trials ESPN (Everolimus versus Sunitinib Prospective Evaluation in Metastatic Non-Clear Cell Renal Cell Carcinoma) and ASPEN (Everolimus versus Sunitinib For Patients With Metastatic Non-Clear Cell Renal Cell Carcinoma), which were designed initially to demonstrate the superiority of everolimus, and the RECORD-3 trial (which included 66 patients with non-clear cell histology), supports the use of first-line sunitinib followed by second-line everolimus as the standard sequence for nccRCC patients, despite possibly biased results.

Other drugs approved for mRCC treatment investigated in non-clear cell histologies include the mTOR inhibitors temsirolimus and everolimus, and the VEGFR-inhibitor sorafenib. Nevertheless, such drugs probably do not represent the best first-line treatment option for the clear cell mRCC population, at least from an actuarial risk point of view according to the International Metastatic RCC Database Consortium (IMDC) model, the true alternative to sunitinib is represented by pazopanib. This VEGFR-TKI is known to be noninferior to sunitinib in terms of efficacy, and has the advantages of favorable safety and quality-of-life profiles, rendering pazopanib still an interesting alternative to be considered even for variant histologies, as suggested by NCCN guidelines.

On the other hand, the new frontier in renal cancer treatment, represented by immunotherapy with CKIs alone (nivolumab) or in combination with each other (nivolumab plus ipilimumab) or with a TKI (axitinib plus pembrolizumab or avelumab), is still at the experimental stage in nccRCC patients, since non-clear cell histologies were excluded from the pivotal trials. The use of immunotherapy for nccRCC is currently restricted to clinical trials, although preliminary results (e.g., with pembrolizumab alone) seem to be promising. In the meanwhile, we should exploit the weapons at our disposal, balancing the (often scarce) amount of evidence with the expected benefits in terms of tolerability and safety.

With the present systematic review, we aimed to report the use of pazopanib in advanced/metastatic nccRCC across the literature, to summarize and provide evidence to possibly support its activity and feasibility in this neglected subgroup of renal cancer patients.

Methods

Search strategy and inclusion criteria
We followed PRISMA guidelines for this systematic review. We searched PubMed for studies published in English language from the inception of each database to 6 August 2019 (see Supplementary Materials for full details). Two investigators (MeB and SB) independently searched the databases. The search terms were [“Carcinoma, Renal Cell” (MeSH) AND “Pazopanib” (Supplementary concept)]. The choice for such a wide search aimed to provide data about the entire pool of publications potentially including patients with nccRCC histology, even as a small subgroup from the overall population considered in each study. After the last selection of publications, we
screened all the references of the included articles for the recovery of any further eligible publications. Furthermore, we screened NCCN guidelines (Version 2.2020) for relevant references on pazopanib in nccRCC.5

Meetings libraries from American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) websites were also screened for further relevant publications (abstract and posters at international meetings), using the search terms “pazopanib” AND “non-clear cell renal carcinoma” OR “papillary renal carcinoma” OR “chromophobe renal carcinoma” OR “collecting duct renal carcinoma” OR “sarcomatoid renal carcinoma” OR “translocation-type carcinoma” OR “medullary renal cell carcinoma” OR “variant histology renal carcinoma”.

Any type of study reporting the use of pazopanib in mRCC including cases with non-clear cell histology was eligible. Non-clear cell histology was defined as any of the following: chromophobe RCC, papillary RCC, collecting duct/Bellini’s RCC, sarcomatoid RCC intended as purely sarcomatoid or with predominant sarcomatoid component (ccRCC with sarcomatoid features was excluded), translocated RCC, medullary RCC or any unspecified non-clear cell histologic variant. We included retrospective studies and prospective trials or case series reporting at least five patients with nccRCC treated with pazopanib. Studies with less than five pazopanib-treated nccRCC patients, single case reports, and reviews without meta-analysis were excluded. Two investigators (MeB and SB) independently reviewed the retrieved publications to select the pertinent articles; disagreements were resolved with the consensus of a third investigator (MaB). Two reviewers (MeB and SB) independently extracted study data; any discrepancies or disagreements were resolved by consensus between all study authors.

As a separate explorative search, we checked clinicaltrials.gov for any trial ongoing with pazopanib in an nccRCC patient population.

Data extraction

The following information was extracted from each study by MeB and SB: first author, year of publication, study type, overall study population (type and number of patients) and setting, number of patients with nccRCC treated with pazopanib and respective histology, line of therapy, primary endpoint/objectives and, if available, pazopanib treatment outcomes in nccRCC patients. We included only the most updated and complete report (full text over posters/abstracts) of any studies when duplicate publications were identified. No statistical analysis was planned due an expected high level of heterogeneity between included studies; instead, findings are descriptive.

Results

Search results

Our search retrieved 305 publications, from which we selected 125 potentially relevant titles for more detailed evaluation (Figure 1). After abstract reading, 61 publications were selected for full-text screening. All their references were screened and a further six publications were included for full-text screening; moreover, another study was recovered from the bibliography of the NCCN guidelines.5 In total, the full text of 68 studies was screened; of these, 13 studies published between 2014 and 2018 met our inclusion criteria and were included in the review.22–34 In addition, eight potentially relevant studies were found as abstract or posters in the ESMO database, of which six were excluded: three were duplicates of fully published articles and three lacked data on histology or had fewer than five nccRCC patients. Two abstracts/posters were included in the review.35,36 Only three potentially pertinent studies were selected from ASCO presentations, but all were excluded (two were duplicates of fully published articles and one did not include any nccRCC patients). Finally, 15 studies were included in the present review, with a total of 318 nccRCC patients treated with pazopanib.22–36

Study characteristics

The heterogeneity was high. Most of the included studies were retrospective (n = 11); one was a retrospective analysis on prospective patient population; the prospective trials (n = 3) included a phase I study, a phase II trial, and a phase IIIb study. No meta-analyses were found. Ten studies included patients with mRCC with different histologies, including ccRCC and nccRCC, while five were conducted in a specifically selected nccRCC patient population. Seven studies included the use of different types of TKI, eight investigated pazopanib (seven as monotherapy and one in combination with another drug). The majority of the studies that included both clear cell and non-clear
cell histologies did not report the outcomes according to the histologic subtype: the only data we could obtain in most of the cases was the number of nccRCC patients receiving pazopanib within the overall patient population. The size of the nccRCC patient population treated with pazopanib across all studies ranged between 6 and 42 patients. The characteristics of the included studies and outcomes data of interest are reported in Table 1.

**Treatment outcomes**

Pazopanib treatment outcomes in nccRCC patients were reported in only four studies. Pazopanib alone as first-line treatment was associated with overall response rates (ORR) of 27% to 33%, disease control rates (partial/complete responses plus stable disease) of 81% to 89%, median progression free survival (PFS) ranging from 8.1 to 16.5 months, and median overall survival (OS) from 17.3 to 31 months. The rate of grade 3–4 (G3-4) adverse events ranged from 21% to 55%. Of interest, the study with pazopanib plus another agent (the histone deacetylase inhibitor abexinostat) was the only one to compare the ORR of nccRCC patients (17%) with that of ccRCC patients (31%); in this study, the histologic subtype was exclusively papillary RCC.
Table 1. Publications included in the review.

| Author of publication and trial name | Study design | Patients (N) | Treatment arm/s | nccRCC patients treated with pazopanib (n) | nccRCC histologic subtype (n) | Line of therapy with pazopanib | Endpoints or objectives (overall population) | Outcome of nccRCC patients treated with pazopanib |
|-------------------------------------|-------------|--------------|----------------|-------------------------------------------|-------------------------------|-------------------------------|--------------------------------------------|------------------------------------------------|
| Escudier *et al.*                 | PISCES      | mRCC, treatment naive (N = 168) | Pazopanib followed by sunitinib versus Sunitinib followed by pazopanib | 12 | Papillary (n = 6) chromophobe (n = 2) other (n = 4) | 1st | Patient preference for a specific treatment (primary endpoint) | NR |
| Vogelzang *et al.*                | Retrospective analysis from US electronic database | mRCC (N = 177) | Pazopanib (followed by mTOR inhibitor as second line in 35 patients) | 32 | NR | 1st | OS, PFS, AEs, treatment patterns, healthcare resource use | NR |
| Pérez-Valderrama *et al.*        | SPAZO       | mRCC (N = 278) | Pazopanib | 18 | NR | 1st | Effectiveness of pazopanib in clinical practice and validation of the IMDC model in this setting | NR |
| Kim *et al.*                     | Single center, retrospective study | mRCC, poor risk features (N = 172) | Pazopanib (n = 72) or sunitinib | 7 | Papillary (n = 3) others (n = 3) unclassified (n = 1) | Prior immunotherapy permitted; prior anti-VEGF therapy excluded | Efficacy and safety of sunitinib and pazopanib in the poor-risk population | NR |
| Ruiz-Morales *et al.*            | Retrospective population-based analysis from the IMDC database | mRCC (N = 7438) | Pazopanib (n = 919) or sunitinib | 29 | NR | 1st | OS, PFS, ORR, performed proportional hazard regression adjusting for IMDC prognostic groups, OS2, PFS2 | NR |
| Joshi *et al.*                   | Single center, retrospective study | mRCC (N = 28) | Pazopanib | 8 | NR | 1st | ORR, PFS, AEs, discontinuations and dose reductions | NR |
| Aggarwal *et al.*                | NCT01543763 Single arm, open label, phase I prospective trial | solid tumors (N = 51), including mRCC patients on dose expansion (n = 22) | Pazopanib plus abexinostat | 6 | Papillary (n = 6) | any | DLT, MTD, AEs, ORR | ORR = 17% (versus 31% in ccRCC patients) |
| Matrana *et al.*                 | Single center, retrospective study | Metastatic nccRCC (N = 29) | Pazopanib | 29 [overall study population] | Papillary (n = 7) chromophobe (n = 4) unclassified (n = 5) other (collecting duct, translocation Xp11.2, sarcomatoid) (n = 13) | any | ORR, PFS, OS, AEs | 1st line: mPFS = 8.1 months; mOS = 31 months; ORR = 33%; subsequent lines: mPFS = 4.0 months, OS = 13.6 months; ORR = 6% G3-4 AEs overall (n = 21) |
| Author of publication and trial name | Study design | Patients (N) | Treatment arm(s) | ccRCC histologic subtype (n) | Line of therapy with pazopanib | Endpoints or objectives (overall population) | Outcome of ccRCC patients treated with pazopanib |
|-------------------------------------|--------------|--------------|----------------|-----------------------------|-------------------------------|-----------------------------------------------|-----------------------------------------------|
| Buti et al. | Multicenter, retrospective study | Multicenter, retrospective study | Papillary (n=19) | Papillary (n=19) | Retrospective registry-based analysis on RENIS registry | Disease control rate (DCR), progression-free survival (PFS), overall survival (OS), adverse events (AEs) | The use of pazopanib as first line increased from 2007 to 2016 (other outcomes NR) |
| Pal et al. | Multicenter, retrospective study | Multicenter, retrospective study | Papillary (n=19) | Papillary (n=19) | Retrospective registry-based analysis on RENIS registry | Disease control rate (DCR), progression-free survival (PFS), overall survival (OS), adverse events (AEs) | The use of pazopanib as first line increased from 2007 to 2016 (other outcomes NR) |
| Jung et al. | Multicenter, retrospective study | Multicenter, retrospective study | Papillary (n=19) | Papillary (n=19) | Multicenter, prospective study on EMO | Disease control rate (DCR), progression-free survival (PFS), overall survival (OS), adverse events (AEs) | The use of pazopanib as first line increased from 2007 to 2016 (other outcomes NR) |
| Poprach et al. | Multicenter, retrospective study | Papillary (n=19) | Papillary (n=19) | Papillary (n=19) | Retrospective registry-based analysis on RENIS registry | Disease control rate (DCR), progression-free survival (PFS), overall survival (OS), adverse events (AEs) | The use of pazopanib as first line increased from 2007 to 2016 (other outcomes NR) |
| Staehler et al. | Multicenter, retrospective study | Papillary (n=19) | Papillary (n=19) | Papillary (n=19) | Retrospective registry-based analysis on RENIS registry | Disease control rate (DCR), progression-free survival (PFS), overall survival (OS), adverse events (AEs) | The use of pazopanib as first line increased from 2007 to 2016 (other outcomes NR) |
Discussion

To the best of our knowledge, this is the first systematic review investigating the use of pazopanib in nccRCC. The first element we came across was the fact that the majority of studies that included a non-clear cell subpopulation completely missed reporting findings for this subgroup of patients; most did not provide results separately according to histology. Beyond the lost opportunity to offer some evidence on the treatment of patients with rare histologies, this constitutes a bias potentially affecting the overall results of such studies within the overall population enrolled, especially given the possible prognostic and/or predictive impact of the ccRCC histologic type.1,37

The limitations of the present analysis are the heterogeneity of the included studies, the limited number of studies with available efficacy data, and the retrospective nature of most of these studies. These limitations may contribute to interpretation bias.

Nevertheless, our analysis provided some useful and favorable elements. First, pazopanib as first-line treatment seems to be consistently associated with an ORR of around 30%. Furthermore, the outcomes of nccRCC patients in terms of PFS and OS showed median values between 8.1 and 16.5 months for PFS, and up to 31 months for OS, which are strongly consistent with those historically known for ccRCC.14,15 Such outcomes are also comparable with those obtained with sunitinib in nccRCC populations.6–9 In addition, the toxicity profile of pazopanib in this subgroup did not appear to be worse than that observed in the pivotal trials of pazopanib in the ccRCC patient population.14,15 On the other hand, the only prospective comparative data between the two drugs have been provided by two studies including ccRCC patients only.14,24 Such outcomes for the latter.14,24 In comparative studies, patients receiving sunitinib were more likely to develop fatigue, hand-foot syndrome, or thrombocytopenia compared with pazopanib, while patients receiving pazopanib were more likely to develop elevated liver enzyme levels.14 Health-related quality of life was higher in the pazopanib than the sunitinib group.14

In the light of such results, in which scenario should nccRCC patients receive pazopanib as the first-line treatment of choice? Of interest, in exploratory analyses from the ASPEN trial, sunitinib was associated with better PFS in patients with favorable or intermediate risk according to Memorial Sloan Kettering Cancer Center (MSKCC) criteria and in those with papillary or unclassified histology.9 In parallel, it should be investigated whether pazopanib should be preferentially offered to patients with other histologic subtypes less responsive to sunitinib. On the other hand, pazopanib may represent a more feasible option for frail or elderly patients considering its good tolerability profile.

NccRCC histotypes still represent a major challenge from a therapeutic standpoint. The authors of an interesting meta-analysis found a negative predictive value of non-clear histology for systemic treatment efficacy in general, with lower response rates, and worse PFS and OS compared with ccRCC; the authors concluded that optimal therapy for patients with non-clear histologies remains to be established.4 Evidence from the present review reinforces this paradigm, as exemplified in the study with pazopanib plus abexinostat, in which the ORR of papillary RCC patients was half that compared with ccRCC patients. On the other hand, our findings seem to be reassuring about the outcome of nccRCC patients treated pazopanib alone. Moreover, across comparative studies, it is hard to determine whether differences in outcomes between nccRCC and ccRCC are due difference in treatment efficacy or to the different biologic behavior of the disease, since it is known that the histologic subtype also influences prognosis.37

On the other hand, new therapies have been recently investigated in advanced nccRCC patients, including immunotherapeutic compounds. The phase II KEYNOTE-427 study of pembrolizumab first-line monotherapy demonstrated an encouraging antitumor activity in the nccRCC cohort (ORR 25.4%).20 Further trials are currently ongoing, such as UNISoN (www.clinicaltrialsgov NCT03177239) and SUNIFORECAST (NCT03075423), both of which are investigating nivolumab with or without ipilimumab in patients with nccRCC. Some of them have preliminary results, with ORR 26% in the nccRCC population for bevacizumab and atezolizumab (NCT02724878),38 and ORR 32% for previously untreated patients in the CALYPSO trial (NCT02819596), which combines savolitinib with durvalumab in patients with papillary...
RCC. Such data suggest similar activity of such new compounds compared with that of pazopanib in the same setting.

Advances in the development of tailored strategies for nccRCC, again mostly observed for the apparent clear cell tumors, are eagerly awaited, especially in the light of the recent identification of their genomic basis and their molecular characterization.40,41 The inclusion of nccRCC, that is, chromophobe, papillary and medullary subtypes of RCC is outside the scope of current knowledge, and, given the spectrum of biology of newly described entities does not permit their inclusion in the same basket of clinical trials in RCC.

Pioneering clinical trials with central identification/classification of tumor histotype including the minimum standards relating to new tumor classification would be welcome.3 New entities (non-clear entities) do express a wide range of angiogenic promoters, thus promising different responsiveness to anti-angiogenic drugs, and also express a wide range of tumoral immune enrichment, again offering a promising target for different immunotherapies.

Trial design for pazopanib in patients with nccRCC should be based on immunophenotypical and molecular analysis of patient tumors, by using CK7, CD10, CD13, PAX-8, HMB45, SDH, cathepsin-K, parvalbumin, and S100A1, with subsequent VHL, chromosome 3p and Xp11, TFE3, and PAX2, PAX8 gene analysis. Large studies in a sample size will provide prospective data in a specific selected nccRCC patient population, potentially offering more strength to the current evidence for the use of pazopanib in this setting.

Of note, at least two trials with pazopanib in this population seem to be ongoing (one completed, but not yet published; Table 2).43,44 Despite their small sample size, they will provide prospective data in a specifically selected nccRCC patient population, potentially offering more strength to the current evidence for the use of pazopanib in this setting.

Conclusion

The systemic treatment of nccRCC is still an unmet clinical need, with few studies in support of an evidence-based choice and sparse guidelines. To date, the main recommendation for a standard first-line treatment supported enough to be the use of pazopanib. However, only a small number of studies support this recommendation, and the evidence is limited. Further studies are needed to confirm the efficacy and safety of pazopanib in the treatment of nccRCC.

Table 2. Trials in progress with the use of pazopanib in advanced non-clear cell renal carcinoma patients.

| Trial number and/or name | Study design | Phase | Disease | Setting | Treatment arms | Estimated enrollment (N) | Primary endpoint | Start date | Estimated completion date |
|--------------------------|--------------|-------|---------|---------|---------------|-------------------------|-----------------|------------|--------------------------|
| NCT0176763643           | Multicenter, single arm, open label | II | Advanced nccRCC (all subtypes) | First or second line | Pazopanib | 38 | 12-month OS rate | 2013 | 2020 |
| NCT0153823844           | Single center, single arm, open label | II | Advanced nccRCC (excluding collecting duct and sarcomatoid) | TKI naive patients (prior immunotherapy permitted) | Pazopanib | 10 | ORR | 2012 | 2015* |

nccRCC, non-clear cell renal-cell carcinoma; ORR, objective response rate; OS, overall survival; TKI, tyrosine kinase inhibitors.

*Completed but not yet published.
reach clinical practice is represented by sunitinib, whilst the strength of evidence being minor for pazopanib as an alternative. Nevertheless, the comparability of pazopanib with sunitinib in terms of efficacy for ccRCC patients is demonstrated, as well as its better tolerability, and the present review provides at least a systematic summary of evidence about its possible use as first line treatment for nccRCC, with favorable outcome despite low strength of evidence. On this basis, we suggest that pazopanib could be considered as a possible good therapeutic option in this setting, aiming to a patient-tailored rather than an exclusively histology-tailored clinical strategy.

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Supplemental material
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