Real-World Treatment with Nivolumab or Cabozantinib for Metastatic Renal Cell Carcinoma (mRCC) in the Veneto Region of Italy: Results of AMOUR Study

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Abstract

Background Second- or third-line treatment options for metastatic renal cell carcinoma (mRCC) have dramatically changed in the last few years. There are no criteria for the choice between nivolumab and cabozantinib, which both demonstrated overall survival (OS) gain in pivotal trials.

Objective We conducted an analysis of oncological outcomes in patients treated in the Veneto Region (Italy), studying different sequences of TKI-nivolumab-cabozantinib or TKI-cabozantinib-nivolumab in a publicly funded healthcare system.

Patients and Methods We conducted a retrospective, real-world analysis of all consecutive patients with mRCC treated with nivolumab or cabozantinib in 2017–2018 at 19 Oncology Units in the Veneto Region.

Results We identified 170 patients, 73 % males, median age 68.4 years. All patients started second-line treatment, 59 % received a third-line therapy. Patients with NLR > 3 had a shorter OS (p < 0.0001). In the second-line treatment, nivolumab was administered to 108 patients (63 %), cabozantinib to 29 (17 %); in the third-line treatment nivolumab was administered to 42 patients (25 %), cabozantinib to 49 (29 %). Median OS and PFS in second line treatment were 28.4 and 6.6 months for nivolumab, 16.8 and 6.6 months for cabozantinib. Median OS and PFS in third-line treatment were 27 and 5.2 months for nivolumab, 16.6 and 7.5 months for cabozantinib. Median OS for nivolumab>cabozantinib sequence versus cabozantinib>nivolumab was 28.8 versus 19.9 months (p = 0.2); median PFS for both the sequences were similar at 5.7 months. A cost effectiveness per month of survival of the two sequences analysis was performed: the cost per month for the nivolumab>cabozantinib sequence was €1738.60 whereas the cost for the other one was €1624.80.

Conclusions In our real-world cohort, most patients received nivolumab as second-line treatment. Outcomes of single drugs are superimposable with those in the published literature. Both the sequences of nivolumab and cabozantinib appear to be viable, effective strategies from an OS and cost-effective perspective.
In a large retrospective cohort of patients, nivolumab and cabozantinib in second- or third-line treatments have an observed median survival that is comparable to published data.

The NLR ratio in the second and the third line treatments confirmed its prognostic power, establishing that the cut-off value of 3 is prognostic even in this setting.

From a cost-effectiveness point of view, the NC sequence was slightly more expensive than the CN sequence, but overall sequence costs per month of OS gain were comparable between NC and CN.

1 Introduction

Globally, renal cell carcinoma (RCC) accounts for 5% of oncological diagnoses in men and 3% in women, with a higher incidence in industrialized countries such as those in Europe and in the USA. While the majority of detected RCCs are still localized and treated surgically, 40% of patients will develop metastases and up to 17% present with advanced disease (metastatic RCC–mRCC) at the time of diagnosis [1].

In the last decade, the therapeutic landscape for mRCC has shifted dramatically, first with tyrosine-kinase inhibitors (TKIs) and later with immunotherapy with check-point inhibitors (CPIs). Meanwhile, immunological treatments with interferon-alfa (α-IFN) or interleukin-2 were gradually phased out due to their excessive toxicity. Sunitinib, a TKI whose main target is the Vascular Endothelial Growth Factor Receptor (VEGF-R), was approved by the US Food and Drug Administration (FDA) in 2006. Sunitinib showed a superior progression-free survival (PFS) and objective response rate (ORR) compared to α-IFN in a large Phase 3 randomized trial [2]. Seven years later, another oral TKI, pazopanib, demonstrated to be non-inferior to sunitinib in a Phase 3 trial [3] with a favorable toxicity profile, was integrated in clinical practice. Options for second- or third-line treatment included axitinib [4], sorafenib [5] and everolimus [6].

New options for second- and third-line treatment have emerged in the last 5 years. In 2015, the first CPI to be experimented in mRCC was nivolumab, a monoclonal antibody which inhibits the programmed-death 1 (PD-1) receptor, thus enhancing the immune-response against cancerous cells. Nivolumab showed a major improvement in OS when compared to everolimus after a first-line therapy with TKIs (25 vs 19.6 months, hazard ratio [HR] = 0.73; 98.5% CI 0.57–0.93; p = 0.002) in the CHECKMATE 025, a randomized, Phase 3 trial. In addition, nivolumab demonstrated a better ORR (25% vs 5%; p < 0.001), but PFS did not differ significantly (4.5 vs 4.4 months; HR = 0.88; 95% CI 0.75–1.03; p = 0.11). With regard to toxicity, nivolumab appeared to be well tolerated with Grade (G) 3 or 4 events occurring in just 19% of patients, versus 37% of the patients receiving everolimus [7].

Nivolumab and several other CPIs were developed for the treatment of mRCC in more recent years, either alone or in combination with other CPIs or TKIs [8]. This development will have a significant impact on the clinical landscape for the optimal management of our patients.

Similarly, cabozantinib was compared to everolimus in patients who had already received therapy with sunitinib or pazopanib (METEOR Phase 3 trial). Cabozantinib is an oral TKI which inhibits VEGF-R as well as cMet and AXL, whose pathways are possible resistance mechanisms to VEGF blockade [9]. In the METEOR study, cabozantinib achieved a median OS of 21.4 months, versus 16.5 months with everolimus (HR = 0.66; 95% CI 0.53–0.83; p < 0.001), and a median PFS of 7.4 versus 3.8 months (HR 0.58; 95% CI 0.45–0.75; p < 0.001). It was approved for use in mRCC after progression to sunitinib or pazopanib [10].

At present, cabozantinib is undergoing rapid development through multiple innovative combinations that are exploring new avenues such as neoadjuvant treatments, novel regimens, and rare RCC histologies [11, 12].

Both nivolumab and cabozantinib were shown to be the better options for second- and third-line treatment after sunitinib or pazopanib, given the OS benefit and the toxicity profile. They have not been directly compared in randomized trials, and the most effective sequence has not yet been established, leaving the decision on second-line therapy to the medical oncologist. Evidence for this choice is limited [13], but after analyzing the impact of the therapies from a pharmacoeconomic perspective, it would seem that nivolumab is the most cost-effective choice, at least in the USA [14]. Indeed, both the EMA and FDA have advocated for the collection of real-world data in post-marketing drug monitoring, as well as the inclusion of economic considerations in the regulatory and approval flow [15]. Available health economics studies are based on efficacy data (e.g., PFS according to RECIST criteria) from pivotal clinical trials, while real-world post-marketing data allow for the construction of a payment by results model. Such models could be extremely useful for accurately assessing the budget impact of novel drugs, and they could entail a price re-modulation, or a reimbursement based on actual results. Cost-effectiveness analysis (CEA) is an important framework for assessing the best value for money across therapies in which
both the costs and consequences of treatment are examined [16]. The introduction of innovative high-cost drugs such as CPIs in the management of mRCC has prompted concerns about sustainability and affordability issue in many countries [17].

In this paper we conducted an analysis of the oncological outcomes (OS and PFS) of mRCC patients treated in the Veneto Region (Italy), examining the reasons for the choice of the second line therapy between nivolumab and cabozantinib. As a secondary endpoint, we evaluated the role of the neutrophils to lymphocyte ratio (NLR) in this setting, as well as the cost-effectiveness (CEA) of different nivolumab-cabozantinib or cabozantinib-nivolumab sequences in a publicly funded healthcare system (Sistema Sanitario Regionale).

2 Patients and Methods

We designed a multicenter, retrospective observational study. All consecutive patients with a confirmed histological diagnosis of RCC commencing second- or third-line treatment with Nivolumab and/or cabozantinib from December 2017 to December 2018 were enrolled, to ensure appropriate follow-up. The patients were treated in the Oncology Units of the Veneto region (Italy). All the region’s Oncology Units cooperate within the Rete Oncologica Veneta (ROV), an integrated system which seek to harmonize the treatment of cancer between the largest (hub) and the peripheral (spoke) centers.

Patient data were retrospectively collected locally on clinical charts, and imputed in a common, anonymized database. All patients started nivolumab or cabozantinib following radiological or clinical evidence of progression to first-line therapy with sunitinib or pazopanib and were treated as per clinical practice. Patients’ prognoses were categorized as good, intermediate, or poor in accordance with the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) [18]. Disease was assessed approximately every 3–4 months, with CT scans of the thorax, abdomen, and pelvis, or with alternative examinations when deemed necessary, according to clinical practice. Adverse events were retrospectively collected based on clinical charts and classified according to the Common Terminology Criteria for Adverse Events (CTCAE v.4.0).

Descriptive statistics on patients’ clinical characteristics were reported, and associations between nominal variables were tested with the chi-square test or Fisher’s exact test (according to the quantity of subgroups). The Kaplan-Meier method was used to evaluate OS and PFS from the start of the second-line treatment to the event of death for any cause or disease progression, respectively. The OS and PFS in different groups were compared using the log-rank test and Cox’s proportional hazards method. After checking the proportionality assumption with Schoenfeld residuals method, variables which showed significance in univariate analysis were compared in multivariate analysis with Cox’s proportional hazard method. All statistical analyses were performed with “R”.

We calculated the cost per patient for nivolumab—cabozantinib and cabozantinib—nivolumab sequences, followed the cost of treatment per median OS month for the two sequences. The model evaluated the mean OS and costs associated with drug acquisition. An economic model was designed and implemented to compare the cost per treated patient and the cost per month of OS. The cost per treated patient only included drug costs based on the different reimbursement mechanisms at the expense used in clinical practice of the regional health system. The cost per median OS month was calculated by dividing the total treatment cost by the number of months to arrive at the median OS for each treatment:

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\text{Cost per Median OS Month} = \frac{\text{Drug Treatment Cost}}{\text{Median OS Months}}.
\]

The study was coordinated by the Istituto Oncologico Veneto (IOV) and was approved by the Ethical Committee on February 10, 2020.

3 Results

One hundred and seventy patients were enrolled in this study from among 19 Oncology Units in our region. Patients’ median age at the time of inclusion in the study was 60.7 years (range 33.3–83.3); the majority were male (72.9%, 124) and 90.6% of patients had clear cell histology. Most of the patients had lung (61.8%) or lymph node (35.6%) metastatic disease. Patients’ demographic characteristics are summarized in Table 1.

By far the most patients received a first-line treatment with sunitinib (115, 67.6%).

All the patients in our cohort received second-line treatment, as per the study’s inclusion criteria. In detail, 108 patients (63.5%) received nivolumab, 29 (17%) received cabozantinib, 16 (9.4%) received axitinib, 11 (6.4%) received everolimus, and 6 (3.5%) received another TKI. Physicians’ reported reasons for the choice of second-line treatment were: the response achieved with first-line therapy (36%), previous experimented toxicities (25%), the need for a change in the mechanism of action (15%), and other/unreported (24%).

The median duration of treatment was 6.6 months for cabozantinib and 6.7 months for nivolumab, respectively.
Sixty-nine patients (40.5%) did not receive a subsequent line of active treatment due to rapid deterioration of their clinical condition and/or death. Most of the remaining patients received nivolumab (42, 41.5%) or cabozantinib (49, 48.5%), while 4 patients were enrolled in clinical trials and 6 patients received a different drug (everolimus or sorafenib). The primary reason for drug choice as third-line treatment reported by physicians was the need to use a drug with positive results in terms of survival (63%). The median duration of treatment in this setting was 7.5 months for cabozantinib and 5.3 months for nivolumab.

The neutrophil to lymphocyte ratio in our population was examined in both second- and third-line treatment. Data were available for 141 patients in the second-line and 86 in the third-line treatment. Patients with a NLR > 3 (40, median OS 11.6 months) at the beginning of second-line treatment had a shorter OS compared to those (101, median OS 43.1 months) with a ratio lower than 3 (p < 0.001, Fig. 1a). Similarly, in the third-line setting, NLR retained its prognostic role (OS 26.5 vs 13.8 months, p 0.01, for NLR >3 and <3 respectively; Fig. 1b).

We also analyzed the second- and third-line survival rates for patients administered nivolumab or cabozantinib. The median OS in the second line was 28.4 months and 16.8 months for patients treated with nivolumab or cabozantinib, respectively. In the third-line setting, the median OS was 27.4 months for patients who received nivolumab and 16.9 months for those administered cabozantinib.

Finally, we analyzed our data according to PFS time. The median PFS in the second-line setting was 5.5 months and 6.3 months for patients treated with nivolumab or cabozantinib, respectively. In the third-line setting, the median PFS was 4.5 months for patients who received nivolumab and 10.0 months for those administered cabozantinib.

Pharmaco-economic aspects were taken into consideration for the subgroup of patients who received the nivolumab sequence followed by cabozantinib or vice versa. We identified 46 patients who received nivolumab during second-line treatment and cabozantinib at disease progression (NC) and 12 patients who were initially treated with cabozantinib and then with nivolumab (CN). When we compared the two different sequences, NC versus CN, we observed a median OS of 28.8 versus 18.9 months, respectively, with a non-statistically significant log-rank test difference (p = 0.3; Fig. 2). We calculated the median time to treatment failure for each
therapy and the median cost per gained month of survival for these subgroups, taking the cost per month of treatment as licensed in Italy at the time of therapy administration (€4202.00 for nivolumab and €3202.00 for cabozantinib.) The median cost per gained month of survival was €1738.60 for the NC subgroup and €1624.80 for the CN subgroup. Detailed data are shown in Table 2.

Finally, we have tried to stratify patients based on risk factors or the first-line treatment received. Unfortunately, due to the sample size and the heterogeneity of the cohort, no subgroup analyses were significant.

4 Discussion

Both nivolumab and cabozantinib are effective treatment strategies for pretreated patients with metastatic renal cell carcinoma, who have progressed to a first-line TKI. However, the lack of validated molecular or clinical predictive factors in this population represents a major challenge for uro-oncologists. There are no direct comparisons between cabozantinib and nivolumab in a second-line setting, and no randomized studies on the optimal therapeutic sequence. In this context, clinical practice data could provide some information to guide clinicians’ choices.

In our real-world setting, which is representative of the Veneto region, we enrolled 170 patients who had received at least second-line treatment for mRCC. This is one of the largest casuistries ever reported and reflects clinical practice in a large and representative Italian region. Of course, this represents a strength of this study, which investigates a real-world setting, without the bias and limitations of the randomized trials. On the other hand, certain limitations should be considered: the retrospective nature of the study, the short period of patient inclusion, in order to obtain significant data in terms of survival; and the rapid scenario changes that are imminent for patients with mRCC.

Demographic characteristics are comparable to those reported in the published literature and do not differ from predicted data [19]. As expected, approximately 40% of the cohort did not receive a third line of active treatment due to rapid deterioration of patients’ clinical condition and/or death, which is consistent with the most recent published data on patients with mRCC progressing to second-line and receiving another active treatment [20, 21].

We analyzed the NLR in second- and the third-line treatments, confirming that the cut-off value of 3 is prognostic even in this setting. The neutrophil count is already incorporated into the IMDC prognostic score for mRCC. Nevertheless, the NLR is a very simple index that can easily be calculated, and its role has been documented [22–24] and could be used in clinical practice to predict survival and aid in the definition of therapeutic strategies.

In addition, we focused on PFS and OS outcomes in our real-world setting. Overall, the observed median survival is comparable to that reported in the data from pivotal trials for nivolumab and cabozantinib [25, 26]. In a recent real-world analysis on cabozantinib published by Santoni et al. [27], the second-line OS was 11.57 months in a global population of 237 patients and the third-line OS was not reached, with a confidence interval starting at 11.51 months. On the other hand, the median OS in our cohort was 16.8 months in the second-line and 16.9 months in the third-line setting. Therefore, our data show a better OS in this setting. This difference could be explained by different patient management, a lower sample size, and possible selection bias. However, our cohort’s OS results are consistent with other retrospective experiences, for instance, Iacovelli et al. [28]. Moreover, our data corroborate those reported by the French early access CABOREAL study [29]. Globally, the

Table 2: Detailed analysis of cost (€) per gained month of OS

|          | TTF 2nd-line tx | Total cost 2nd-line tx | TTF 3rd-line tx | Total cost 3rd-line tx | Grand total cost | Median OS of the sequence | Cost per gained month of OS |
|----------|----------------|------------------------|----------------|------------------------|-----------------|---------------------------|-----------------------------|
| NC       | 5.6            | 22,534.40              | 8.6            | 27,537.20              | 50,071.60       | 28.8                      | 1738.60                     |
| CN       | 5.9            | 18,891.80              | 3.3            | 13,279.20              | 32,171.00       | 19.8                      | 1624.80                     |

OS overall survival, TTF time to treatment failure, tx treatment
OS reported by real-world observational protocols is inferior compared to the updated data of the pivotal METEOR trial (21.4 months) [25]. However, it is well known that patients enrolled in randomized trials are accurately selected and may significantly differ if compared with the broad population of patients receiving health care in clinical practice, as a result of stringent eligibility criteria (for instance, good performance status, absence of clinically relevant concomitant diseases, etc.) [30].

Similar considerations can be made for the observed survival data of nivolumab in our cohort, which was congruent with the results of the CheckMate 025 trial [26]. Our cohort performs better than other real-world cohorts [31, 32] and is in line with the data from the Italian Nivolumab Expanded Access Program [33].

We present data on a real-world population treated in a publicly funded health system with "universal access" to healthcare. From a cost-effective point of view, the NC sequence was slightly more expensive than the CN sequence (€1738.6 vs €1624.8 per month of OS). The difference in OS between the two sequences was not statistically significant in our cohort, despite the presence of a trend favoring NC (28.8 months of OS vs 18.9 months of CN). Interestingly, time to treatment failure (TTF) was longer with the NC sequence (8.6 vs 3.3 months), leading to a higher overall therapy cost. However, the longer OS documented in our cohort for patients treated with nivolumab in a second-line setting and cabozantinib in the third-line setting compensated for this, resulting in a similar cost per month of OS for the two treatment strategies. The issue of expensive therapies in the advanced setting for mRCC has been analyzed in different countries and health systems, and in recent years, different sequences of the first- and second-line therapies have been analyzed from a cost-effectiveness perspective [34–36]. To date, nivolumab and cabozantinib have yielded the best results in terms of PFS and OS in second- and third-line settings when compared to everolimus, even if costs for the health system are higher. Additional cost-effectiveness studies are required in the near future, given the recent introduction of combination therapies in first line, such as pembrolizumab + axitinib [37] and nivolumab + cabozantinib [38], which are even more expensive and are rapidly changing the scenario for mRCC patients.

5 Conclusions

Cabozantinib and nivolumab were the most used treatments for second- and third-line treatment mRCC in our real-life multicenter experience. Both the NC and CN sequences proved to be effective, with PFS and OS results comparable to those of clinical trials. Even though the difference in OS was not statistically significant, the NC sequence demonstrated a slight improvement in OS. The NLR ratio confirmed its prognostic power, in each treatment line, regardless the drug. Sequence costs per month of OS gain were comparable between NC and CN.

Declarations

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Conflict of interest MM received consulting or advisory board fees from Bristol Myers Squibb, Janssen Cilag, Astellas, IPSEN, Merck Serono, MSD, and Pfizer. VZ received consulting or advisory board fees from Bristol Myers Squibb, Janssen Cilag, Astellas, IPSEN, Roche, MSD, Lilly, and AstraZeneca. The other authors FP, AB, DP, AZ, MN, DS, RDV, FZ, DB, DP, GDV, MS, MB, CM, PR, CB, GP, and UB have disclosed no conflicts of interest that are relevant to the content of this manuscript.

Ethics approval The study was coordinated by the Istituto Oncologico Veneto (IOV), and was approved by the Ethical Committee on February 10, 2020, with consent to participate and for publication.

Availability of data and material The original dataset was collected and stored by MM, who is responsible for the data’s integrity.

Authors’ contributions Study conceptualization and design: MM, VZ, UB, AB; Data acquisition: DP, AZ, MN, DS, RDV, CM, FZ, PR, CB, GP, and UB.; Statistical analysis: FP, MB, UB.; Interpretation of the data: All authors; Drafting of the manuscript: MM, FP, UB, MB; Critical revision of the manuscript for important intellectual content: All authors; Final approval of the manuscript: All authors.

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