Original Study

Long-term Clinical Outcomes of a Spanish Cohort of Metastatic Renal Cell Carcinoma Patients with a Complete Response to Sunitinib

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Abstract

Sunitinib, a tyrosine kinase inhibitor, has been central for the treatment of metastatic renal cell carcinoma until the recent development of immunotherapy. This study analyzed the characteristics of patients with complete response to sunitinib (n=62) to understand associations with clinical variables. A complete response to sunitinib could be achieved irrespective of prognostic group, metastasis site or histology type.

Introduction: The long-term clinical outcomes of patients with metastatic renal cell carcinoma (mRCC) and a complete response (CR) to the tyrosine kinase inhibitor (TKI) sunitinib are poorly known. The characteristics of these patients

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could reveal previously undetected associations with clinical variables. **Patients and Methods:** This observational, retrospective study (ATILA) used data from a registry of patients with mRCC who had received first-line sunitinib and had achieved CR from 2007 to 2018 in Spain. **Results:** Sixty-two patients with CR were included; 48 patients (77.4%) received sunitinib in monotherapy and 14 (22.6%) combined with or followed by local treatment. Median age was 58.5 years (range, 32–81). Most patients (79.0%) had clear cell histology and had undergone previous nephrectomy (90.3%). The majority (70.2%) had an intermediate IMDC prognosis, 23% favorable and 7.0% poor. The median time on treatment with sunitinib was 28.2 months (IQR, 16.7–41.0) and the median time to CR was 10.9 months (IQR, 7.2–19.3). After a median follow-up of 8 years (range, 3–13 years), the median PFS was not reached. The overall median duration of complete response was 64.1 months (IQR, 32.2–99.4). The tolerance and safety profile of sunitinib was consistent with previous reports. **Conclusion:** Durable CR to sunitinib was observed in patients regardless the prognosis group, metastasis site or histology type, with 75% of patients remaining in CR after 10 years. Clinicaltrials.gov: NCT03916458.

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Introduction

Renal cell carcinomas (RCC) account for about 2% of global cancer diagnoses and deaths, and for >80% of all cancers in the kidney.[1] Survival depends strongly on the stage at diagnosis, with metastatic RCC (mRCC) having a 12% survival rate at 5 years.[2]

Current first line standard treatment for mRCC is based on various combinations of either immune checkpoint inhibitors (ICIs) such as ipilimumab/nivolumab or ICIs with tyrosine kinase inhibitors including pembrolizumab/axitinib, avelumab/axitinib, pembrolizumab/lenvatinib, and nivolumab/cabozantinib.[3–6] The mixed therapies approach benefits from the antiangiogenic activity of the TKI targeting vascular endothelial growth factor, and the ICI targeting the immune system signaling cascade. Combination therapies have revolutionized clinical treatment of mRCC with high rates of durable responses.[7,8]

Since its FDA approval in 2006 and until the recent introduction of combination therapies, the oral TKI sunitinib has been a standard of care for first-line mRCC therapy.[9,10] All recent phase 3 clinical trials have considered sunitinib as the standard comparator arm.[4,11–13] A retrospective study with a long follow up found a median overall survival (OS) of 4.3 years in patients with clear cell histology, favorable International mRCC Database Consortium (IMDC) risk score, and receiving first-line sunitinib.[14] Although long-term responses has been observed after treatment with sunitinib in clinical trials[15,16] and observational studies,[17,18] a complete response (CR) is rarely achieved. Rates of CR of up to 3% were found in the pivotal clinical trials and the expanded access programs of sunitinib,[19–21] and were comparable among TKIs.[22] Similar rates of CR for sunitinib have been reported in the retrospective real-life studies, with values of 3.6%,[23] or even 6.1%.[24] Recent phase 3 trials in which sunitinib was used as the comparator found rates of CR of 1.8–4.6%.[4,12,13] In contrast, the experimental TKI- and ICI-based combinations reach CR rates of 8 to 16%.[25]

The characteristics of patients achieving CR during treatment with a TKI are not well defined. A meta-analysis of CR including all TKIs found no associations between the rates of CR and other clinical variables.[22] For sunitinib, CR has been observed after treatment combined with local treatment, and in patients with metastasis at any site and in every prognostic group.[24] Although no additional safety risks have been reported for the long-term treatment with TKI (up to 6 years),[16] there are no guidelines on the therapeutic strategy to be followed in these cases.

The primary objective of this study was to describe the characteristics of patients treated with first-line sunitinib that achieved CR in daily clinical practice. A combined analysis of a large cohort could provide insights on previously undetected associations with clinical variables in this group of patients.

Materials and Methods

The ATILA study was a post-authorization, observational, retrospective, multicenter study of patients with mRCC who had received sunitinib as a first line treatment according to the drug's indication and achieved a CR between 2007 and 30th September 2018 in Spain. The objective was to describe the characteristics of patients achieving a CR in daily clinical practice and to search for clinical associations between CR and baseline characteristics of both the patient and the tumor, and their correlation with the treatment and outcomes. The study was conducted at 30 public and private hospitals throughout Spain between December 2019 and November 2020. As the study used unstructured anonymized data, no informed consent was obtained from the patients, except when the local Ethics Committee required it (5 sites). In these cases, in the event that the patient continued to attend routine reviews at the hospital, the physician in charge communicated the patient a privacy alert according to the new EU legislation on personal data (2016/679 of the European parliament). The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University Hospital 12 de Octubre (protocol code A-6181227, 29 October 2019).

Patients

The patients had to meet all the inclusion criteria to participate in the study: age ≥18 years, treated with first-line sunitinib for mRCC (prior cytokine therapy was accepted) and achieved a total disease remission as best response according to investigator assessment from a clinical, radiological and/or macroscopic perspective. This response must have been achieved through two possible strategies: systemic treatment with sunitinib alone or treatment with

sunitinib and subsequent local treatment for one or several residual lesions that have not completely responded to the drug (traditional surgery, radiotherapy, stereotactic body radiation therapy). CR should be confirmed by at least 2 consecutive imaging tests with no limit on the duration of this response (patients with subsequent progression could be included in this registry.

Patients were excluded if they had been treated with other drug different from sunitinib, had no local radiology reports that confirmed the CR; had no record of the sunitinib dose and regimen received; or if the CR was achieved after 30th October 2018.

Study Procedures

Decisions on treatment depended solely on the treating physician's clinical judgement. As this was a retrospective observational study designed to reflect routine clinical practice, there was no interference with the daily routine of care to the patients. No patient follow-up period was established and there were no patient interviews. Patient's data was only reviewed when the investigator completed his/her paper CRF.

The following variables were recorded: anonymized demographic data, medical history (including date and stage of disease at diagnosis and at progression), surgical treatment, histology, disease risk criteria before its onset, comorbidities, blood count and blood clinical chemistry, history of treatment with sunitinib, associated adverse events (AEs), clinical efficacy, dose, treatment start date and subsequent treatments, as well as the patient's condition (alive, deceased) and the last date on which contact was made.

Statistical Methods

All baseline demographic and clinical characteristics were summarized descriptively. The categorical variables were described by means of their absolute and relative frequencies. Continuous variables were described using measures of centrality and dispersion: mean, 95% confidence interval (95% CI), standard deviation, median, 25th and 75th percentiles, minimum and maximum, including the total number of valid values.

The criterion pertaining to the follow-up time until the event of interest (complete disease remission, disease progression, change of treatment due to unacceptable toxicity or death from any cause) was described by estimating survival functions using the Kaplan-Meier method. Specific estimates and 95% confidence intervals were provided for the median, 25th percentile and 75th percentile of this variable. Progression-free survival (PFS) was calculated as the time elapsed from the date of the first CT scan until the date of progression/death, if applicable, or otherwise it was censored on the date of the last patient follow-up. To find associations between time to CR and the baseline features of both patient and tumor, a log-rank test was used to compare the groups and determine the statistical significance of the correlation between each of the baseline variables and the time to complete remission of disease.

For the safety analysis of treatment with sunitinib, the percentage of patients who experienced serious and non-serious AEs explicitly attributed to sunitinib during treatment was analyzed descriptively. The frequency of AEs recorded was reported based on seriousness, severity and whether it or they led to suspending or adjusting the dose.

Table 1 Characteristics of the Patients at the Start of Treatment (n=62)

Variable	n=62
Age, years, mean (range)	58 (32–81)
Age range, years	
<65	42 (67.7)
65–74	17 (27.4)
≥75	3 (4.8)
Time from diagnosis, months, median (IQR)	2.3 (1.3–6.8)
Histology, N (%)	
Clear cell	49 (79.0)
Non-clear cell	5 (8.1)
Sarcomatoid	7 (11.3)
NA	1 (1.6)
Prior nephrectomy, N (%)	56 (90.3)
Local treatment, N (%)	14
Standard surgery	13 (21.0)
Stereotactic body radiation therapy	1 (1.6)
Neutrophil/lymphocyte ratio, N (%)	
<3	44 (75.9)
≥3	14 (24.1)
ECOG, N (%)	
0	38 (61.3)
1	22 (35.5)
2	1 (1.6)
NA	1 (1.6)
Prognostic group (IMDC), N (%)	
Favorable	13 (22.8)
Intermediate	40 (70.2)
Poor	4 (7.0)
Organs affected, mean (range)	1.6 (1–4)
Organs affected, N (%)	
1	32 (51.6)
2	25 (40.3)
≥3	5 (8.1)
Metastatic sites, N (%)	
Lung	42 (67.7)
Lymph nodes	23 (37.1)
Muscles, soft tissues, vessels and peritoneum	8 (12.9)
Liver	6 (9.7)
Bone	6 (9.7)
Endocrine glands	6 (9.7)
Other	9 (14.5)
Main comorbidities, N (%)	
Cerebrovascular disease	29 (46.8)
Obesity	11 (17.1)
Renal failure	5 (8.1)
Other	32 (51.6)

Abbreviations: ECOG = Eastern cooperative oncology group; IMDC = International metastatic renal cell carcinoma database consortium; IQR = interquartile range; NA = not available.

Table 2 Time to CR and Duration of CR

	Overall	Sunitinib Monotherapy	Sunitinib + Local Treatment
Time to CR	10.9 (7.2–19.3)	10.5 (6.6–18.2)	17.8 (7.9–30.5)
Age <65 years (n=42)	10.0 (6.8–18.4)	10.0 (4.0–18.2)	8.3 (7.2–19.4)
Age ≥65 years (n=20)	15.4 (9.5–19.7)	13.3 (9.1–18.1)	30.5 (17.2–33.2)
Duration of CR	64.1 (32.2–99.4)	69.8 (32.2–100.1)	58.4 (28.3–80.5)

All values are expressed as median (IQR) months.
Abbreviation: CR = complete response.

In all cases, a level of statistical significance of 0.05 was employed.

Results

Patient Characteristics at the Start of Treatment

Sixty-two patients with mRCC who experienced CR during treatment with sunitinib were identified and included in the study. The mean age of the participants was 58 years (range, 32–81 years) and most patients (67.7%) were under 65 years of age at the start of treatment (Table 1). The median time from disease diagnosis to the initiation of sunitinib treatment was 2.3 months (IQR, 1.3–6.8). The most prevalent histological type was clear cell renal cell carcinoma, found in 49 patients (79.0%). Five tumors were classified as no clear cell histology and 7 (11.3%) had sarcomatoid features.

At the start of treatment, 61.3% had an ECOG score of 0 (Table 1). Most patients (70.2%) had an intermediate prognosis according to the IMDC risk score, 22.8% were favorable and 7.0% had a poor prognosis. The median number of metastases was 2. The most common site of metastasis was the lungs (67.7%). Nephrectomy had been previously performed in 56 patients (90.3%). Among the 40 patients with comorbidities, cardiovascular disease and obesity were the most common, at rates of 46.8% and 17.7%, respectively. The neutrophil/lymphocyte ratio before treatment was <3 in 44 out of 58 patients (75.9%).

Treatment with Sunitinib

Most patients (n=48, 77.4%), received sunitinib monotherapy, and 14 patients (22.6%) received an additional local treatment to achieve CR. The median time on treatment with sunitinib was 28.2 months (interquartile range [IQR], 16.7–41.0).

Out of the 62 patients included, 59 patients (95.2%) started sunitinib at a dose of 50 mg compared to 4.8% who received sunitinib at an initial dose of 37.5 mg. All but one patient (98.4%) started sunitinib with a 4/2 regimen (4 weeks with sunitinib and a 2-week break). The median time from the start of treatment to the first CT scan showing disappearance of all lesions was 10.9 months (IQR, 7.2–19.3) (Table 2). The median duration of treatment with sunitinib once CR was achieved was 22.1 months (IQR, 8.5–32.5) and the median duration of CR was 64.1 months (IQR, 32.2–99.4).

After a median follow up of 99 months (range, 36–159), 12 patients continued sunitinib treatment and 46 interrupted sunitinib treatment because of CR (n=16), disease progression or death (n=13) and other causes (n=21). The median PFS was not reached (Fig. 1) and 75% of patients were free of disease progression after 10 years.

No statistically significant differences in terms of duration of CR were found between patients on sunitinib monotherapy and patients on sunitinib plus subsequent local treatment (P >0.05; Mann–Whitney U test).

Subgroup Analysis

An analysis of efficacy by subgroups was performed according to age, prognostic criteria, metastasis, Fuhrman grade, histological type, treatment type, and toxicities. In the univariate analysis, the only predictive factor for PFS and duration of CR was age (<65 years versus ≥65 years), with the median PFS not achieved for the younger patients versus 97.3 months for those >65 years of age (P=0.037) and the median duration of CR not achieved versus 83.8 months (P=0.043), respectively (Figure 2). Although not statistically significant, the median time from starting treatment to achieving CR was 15.4 months in the ≥65-year-old group and 10.0 months in the <65-year-old group (Table 2).

Safety

For the analysis of safety, the AEs were recorded as per the highest grade assessed by investigators. A total of 248 AEs were recorded in 51 patients at some point during the treatment with sunitinib (Table 3). Of these patients, 22 experienced grade 1-2 toxicity, 28 patients grade 3-4, and the information was not known in 1 patient. The most common AEs were fatigue (48.4% of patients), palmar–plantar erythrodysesthesia (PPE) (40.3%) and mucosa inflammation (33.9%). Grade 3-4 AE were fatigue in 12.9% of patients, PPE in 9.7%, hypertension in 9.7%, neutropenia in 8.1%, and diarrhea in 3.2%. Nine patients (14.5%) experienced a serious AE, 6 patients a single AE and 3 patients two AEs. A total of 97 AEs in 49 patients led to discontinuation and/or dose adjustments. No connection was found between the onset of AEs and response to treatment.

In total, 50 patients (80.6%) of the patients required dose and/or regimen adjustments; 66% dose reductions and 28.4 % with scheme modifications. The median time from the start of treatment until the first dose adjustment was 5.7 months.

Forty-seven patients (75.8%) had a total of 111 dose interruptions. On 63 occasions (56.8%), the reason for interrupting the treatment was toxicity; on 21 occasions (18.9%), it was complete response; on 22 occasions (19.8%), it was another reason; and on the 5 remaining occasions it was some combination of the above. The median total days of discontinuation was 42 days (IQR, 26.0-108.0), including 15 cases who did not resume the treatment.

Figure 1 PFS. There were 15 events (24.2%) and 47 censored (75.8%). The median was not reached

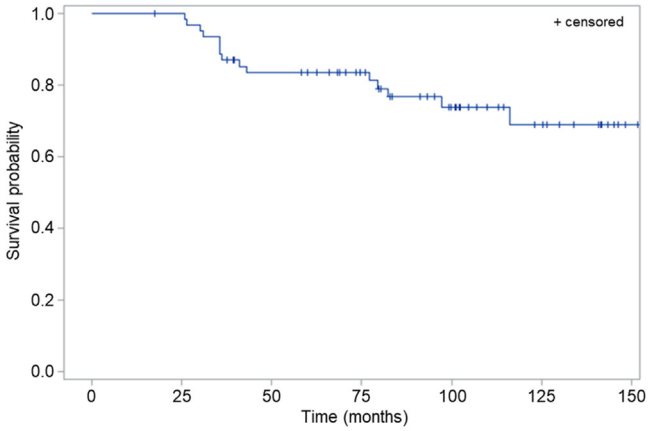


Figure 2 PFS (A) and duration of CR (B) by end age. Statistically significant differences were found in PFS and duration of CR (P=0.0377 and P=0.0430 respectively, Log-Rank test) between young patients (<65 years) and elderly patients (≥65 years). Abbreviations: PFS, progression-free survival; CR, complete response

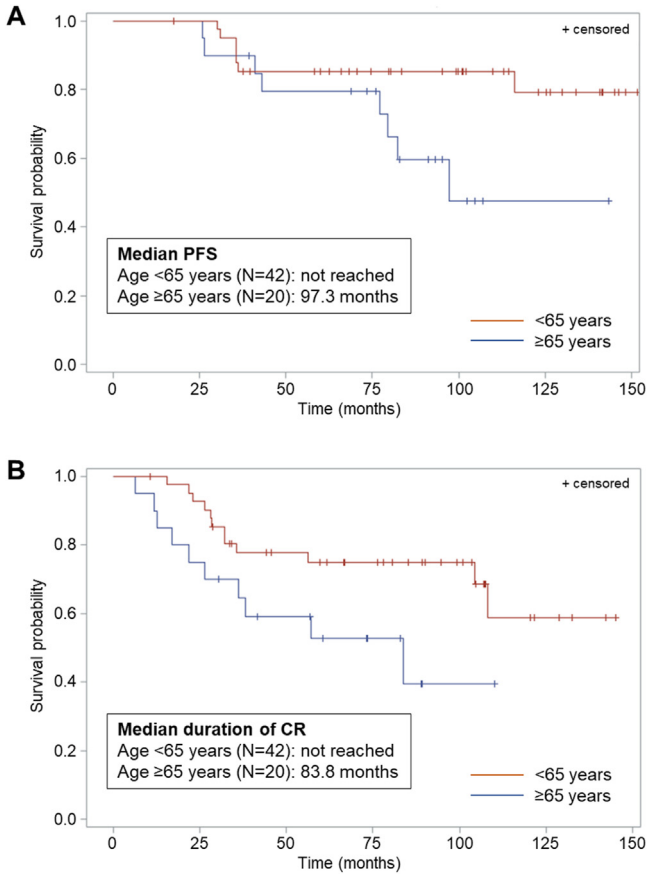
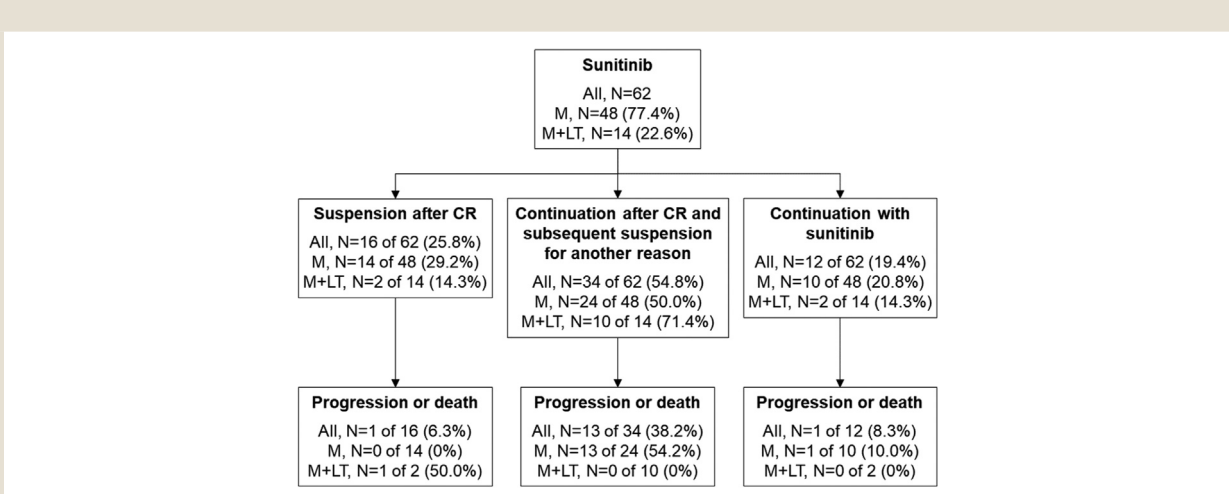


Table 3 Common Adverse Events (Occurring in at Least 10% of Patients)

Toxicity	Grade 1-2	Grade 3-4	Total
Fatigue	22 (35.5)	8 (12.9)	30 (48.4)
Palmar-plantar erythrodysesthesia syndrome	18 (29.0)	6 (9.7)	25* (40.3)
Mucosal inflammation	21 (33.9)	0	21 (33.9)
Diarrhea	20 (32.3)	2 (3.2)	22 (35.5)
Hypertension	14 (22.6)	6 (9.7)	20 (32.3)
Hypothyroidism	9 (14.5)	0	10[b] (16.1)
Dysgeusia	9 (14.5)	0	9 (14.5)
Neutropenia	3 (4.8)	5 (8.1)	8 (12.9)
Eyelid edema	5 (8.1)	0	6* (9.7)
Yellowish skin	5 (8.1)	0	5 (8.1)
Dyspepsia	3 (4.8)	0	4[a](6.5)
Decreased appetite	4 (6.5)	0	4 (6.5)

All percentages calculated over the total number of patients (n=62).
[a] Grade not available for some patients.

Figure 3 Changes over time in continuity or discontinuation of sunitinib for the whole cohort (n=62), patients in monotherapy (n=48), and patients receiving sunitinib and subsequent local treatment (n=14). Local treatment included surgery, radiotherapy, or stereotactic body radiation therapy. Abbreviations: CR, complete response; M, monotherapy; M+LT, monotherapy and sub-sequent local treatment



Patients who developed fatigue required a median of 13.5 months to achieve CR versus 8.5 months in those who were not fatigued (P=0.0467).

Of all 62 patients, 16 patients (29.2%) discontinued the treatment after achieving CR. Of the 46 who continued with treatment, 12 (26.1%) remained on treatment at the time of the analysis, 34 patients (73.9%) discontinued the treatment, 9 of them (26.5%) due to toxicity, 11 (32.4%) due to progression and 14 due to other reasons.

Treatment After Sunitinib

The treatment changes over time for all patients included in the study are shown in Fig. 3. Of all 62 patients, 16 patients (29.2%) discontinued the treatment after achieving CR. Of the 46 who continued with treatment, 12 (26.1%) continued with sunitinib as first-line treatment; the remaining 34 patients (73.9%) discontinued the treatment, 9 of them (26.5%) due to toxicity, 11 (32.4%) due to progression and 14 due to other reasons.

Among the 50 patients who stopped sunitinib, 17 patients received another second-line treatment after disease progression: 10 patients switched to another TKI (58.8%), 6 patients were treated with immunotherapy (35.3%) and 1 patient with a mTOR inhibitor (5.9%).

Discussion

This observational study provides aggregated information of a national cohort of 62 patients achieving sustained CR after treatment with sunitinib for mRCC, with the goal of describing

their clinical characteristics and to correlate them with treatment outcomes and therapy. The results show that disappearance of all macroscopic lesions was associated with a duration of CR of >10 years in 3 out of every 4 patients, and that patients aged <65 years presented longer PFS and duration of response than older patients. The tolerance and safety profile of sunitinib was consistent with previous published reports.

At the start of treatment, 70.2% of patients who achieved CR in this series were classified with an intermediate prognosis according to the IMDC risk score, highlighting the role of antiangiogenic drugs in this group of patients. Interestingly, in this cohort, four patients with poor IMDC risk score also achieved CR. No differences in the subgroup analysis were found between the risk groups in terms of long-term outcomes, following on similar observations from previous studies.[24,26] Interestingly, 11.3% of patients in our study achieved CR despite sarcomatoid differentiation. While current standard of care for these patients is immunotherapy, our observation suggests that some patients may benefit from a combination of IO/TKI.

The median time on treatment with sunitinib until achieving complete remission of the lesions according to investigator assessment was 10 months, in line with findings published by other authors.[23,24] The median duration of response was 64.1 months, with a minimum of 6.3 months and a maximum of 145.2 months (12.1 years) and about 75% of patients were progression-free at 10 years. No differences in disease recurrence were found between patients who had continued or discontinued treatment after achieving CR to sunitinib (P=0.32). The univariant analysis by age subgroups provided valuable information on outcomes in patients over 65 years of age (20 cases), showing significant differences and worse outcomes in PFS and duration of CR.

Regarding the tolerability of the treatment, all patients over 65 years had AEs, most of which resulted in dose adjustments and discontinuations. No large differences were identified between the number of dose modifications or interruptions between the general population and those ≥65 years of age (20 patients). The median time until the first dose modification was shorter in patients ≥ 65 years of age, 2.8 months (95% CI 2.3–7.4) vs 5.7 months in the general population (95% CI, 5.9–9.5). Grade ≥3 AE analysis comparing the general population with the group ≥65 years of age showed a similar tolerability profile with neutropenia in 5 (8%) vs 2 (10%) patients and fatigue in 9 (14.5%) vs 5 (25%) patients, hypertension in 7 (11%) vs 4 (20%) patients and PPE in 7 (11.3%) vs 8 (40%) patients, noticeably more frequent in the older population. The results of this study demonstrate a similar treatment safety profile between the population ≥65 years of age and the general population, although particular care should be taken with regard to the onset of PPE in this group. These results contrast with some retrospective reviews that did not identify differences in terms of efficacy and tolerability by age.[27,28]

Given the consistently low percentage of patients achieving CR, it is somewhat surprising that no common clinical characteristics have been found among them.[24] Better molecular characterization is necessary to determine which patients may benefit from therapy with a TKI alone. Recent trials have identified an 'angiogenesis-high' genetic signature present in higher frequency in the favorable risk group which correlated with increased PFS benefit to sunitinib.[29–31] In these studies, the genetic signature was enriched with genes associated with the VEGF pathway targeted by sunitinib. However, the clinical utility of these biomarkers remain uncertain since all clinical IMDC groups may present with angiogenesis-high signatures. Also immunotherapy has been shown to be useful in patients with angiogenesis-high signatures.[30]

Although generally the combination of TKI and ICI has demonstrated an OS benefit over sunitinib in all IMDC patient risk groups in the phase III pivotal trials,[11–13,32] the heterogeneity of RCC patients often leads to a high variability in responses to combination treatments.[8,33,34] Due to the very limited number of predictive biomarkers used in clinical practice, making the combination treatment extensive to all mRCC patients could result in increased toxicity and limit the therapeutic arsenal for subsequent lines of treatment. The efficacy and tolerability of TKIs in second line after ICI was comparable TKI in first line in a retrospective study.[35] For these reasons, some authors have recently argued that first-line TKI monotherapy can still be considered the best therapeutic choice for a selected group of patients.[36,37] These could include, for example, patients with a clearly defined angiogenic profile, or patients who are ineligible for combination treatment due to comorbidities or frailty.[37] In addition, de-scalation therapy is a strategy that may be highly relevant for patients and health systems. Understanding which patients may benefit from only one drug compared to combinations or can stop one of the therapies remain key questions in clinical practice.

As all retrospective studies, this analysis was limited by its post hoc nature, which could lead to bias and patient heterogeneity. For example, 22% of patients achieved CR after additional local treatment, which could have added bias to the population studied. The lack of independent radiologic review could have resulted in the inclusion of false negatives, although this makes the study more applicable to real clinical practice. Also, since patients on TKI monotherapy achieving CR are rare, the subgroup analysis was unbalanced for some groups, which may have limited the statistical analysis. However, registries are valuable tools to collect data under real-world conditions in low-frequency and poorly characterized groups of patients, such as the one described here.

Conclusions

Consistent with previous reports, this study found that long term CR was achieved regardless of IMDC prognostic group and metastasis site. The patients were maintained on sunitinib treatment for a median of 22.1 months after CR, and there were no differences in PFS between patients who stopped or continue sunitinib treatment after CR was achieved. The CR was durable (median 5.34 years), whether treated with sunitinib monotherapy or with sunitinib followed by local therapy. In this cohort of patients, the only clinical variable associated with increased PFS and longer duration of CR was age <65 years.

Clinical Practice Points

TKIs have been the basis for the treatment of mRCC until the recent development of immunotherapy. Some patients present a sustained complete response to first-line treatment with the TKI

sunitinib. The ATILA study analyzed the characteristics of these patients to gain insights on previously undetected associations with clinical variables and to help the development of therapeutic recommendations for this group of patients. The study found that a complete response to sunitinib could be achieved irrespective of the prognostic group, metastasis site or histology type. Although first line sunitinib has been mostly replaced by combination ICI or ICI/TKI therapies, certain patient populations may still benefit from therapies with sunitinib. First-line TKI monotherapy could still be considered the best therapeutic choice for patients who are ineligible for combination treatment due to comorbidities or because of frailty. In some circumstances, de-scalation from combination therapy could be the best therapeutic choice for a variety of clinical reasons. Also, some developing countries could have limited access to combination therapies, and could continue use of TKIs in all or part of the patients. Continuous work identifying patterns and behavior of extreme responders, such as patients achieving CR, should help physicians tailor treatment in the future.

Authors' Contributions

Conceptualization, Guillermo de Velasco and Úrsula Asensio; Methodology, Guillermo de Velasco, Teresa Alonso-Gordoa, Alejo Rodríguez-Vida, and Úrsula Asensio; All authors contributed to research; Supervision, Guillermo de Velasco, Teresa Alonso-Gordoa, and Úrsula Asensio; Writing (original draft preparation), Guillermo de Velasco and Úrsula Asensio. All authors reviewed and edited the manuscript; all authors read and agreed to the published version of the manuscript.

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G.A.P. served in speaker bureaus for Ipsen, BMS, Roche, and Janssen.

M.C. served in advisory or consultancy roles for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, EUSA Pharma, Lilly, Roche; received honoraria for lectures for Abbot, Bristol-Myers Squibb, EUSA Pharma, Ipsen, Novartis, Pfizer, Pierre Fabre, Roche; holds institutional financial interests in Astra Zeneca, Merck, Pfizer, Roche, and received travel expenses from Ipsen, Lilly, Merck, Pfizer, and Pierre Fabre.

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