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Sorafenib as First- or Second-line Therapy in Patients With Metastatic Renal Cell Carcinoma in a Community Setting

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Abstract and Introduction

Abstract

Aim The Italian Retrospective Analysis of Sorafenib as First or Second Target Therapy study assessed the efficacy and safety of sorafenib in metastatic renal cell carcinoma patients treated in the community.

Patients & methods Patients receiving first- or second-line single-agent sorafenib between January 2008 and December 2010 were eligible. Retrospective data collection started in 2012 and covers at least 1-year follow-up. The primary end point was overall survival (OS).

Results Median OS was 17.2 months (95% CI: 15.5–19.6): 19.9 months (95% CI: 15.9–25.3) in patients treated with first-line sorafenib and 16.3 months (95% CI: 13.1–18.2) with second-line sorafenib. Overall median (95% CI) progression-free survival was 5.9 months (95% CI: 4.9–6.7): 6.6 (95% CI: 4.9–9.3) and 5.3 months (95% CI: 4.3–6.0) in first- and second-line patients, respectively.

Conclusion The efficacy and safety of sorafenib in routine community practice was generally good, especially in relation to OS in patients treated in the second line, where results were similar to those seen in recent prospective clinical trials.

Introduction

Drugs that target signaling pathways involved in tumor proliferation and angiogenesis have transformed the treatment of metastatic renal cell carcinoma (mRCC).[1] In January 2005, the tyrosine kinase inhibitor (TKI) sorafenib was shown to extend progression-free survival (PFS) significantly[2] and also prolong overall survival (OS)[3] relative to placebo. In 2005, this agent was the first TKI approved worldwide for mRCC by the US FDA. Since then, a further three TKIs/VEGF receptor inhibitors (sunitinib, pazopanib and axitinib), a monoclonal antibody (bevacizumab, in combination with interferon [IFN]) and two mTOR inhibitors (temsirolimus and everolimus) have been approved for mRCC on the basis of randomized controlled trials.[4–9]

Following registration based on the TARGET trial,[2,3] clinical experience with sorafenib has grown in both the first and second line (defined as the initial and second systemic antitumor target therapy received, respectively), and it has performed well in relation to previous studies and compared with investigational agents.[10] In an early first-line trial, sorafenib and IFNα-2a resulted in similar PFS (5.7 vs 5.6 months, respectively), although sorafenib was better tolerated and patients in this arm had a better quality of life.[11] In the most recent data comparing sorafenib with tivozanib as first-line therapy in patients who received no or one prior systemic therapy (cytokines) for mRCC (70% in both arms were naive to systemic therapy), the primary end point, median PFS in the total population, was 11.9 months with tivozanib and 9.1 months with sorafenib ($p = 0.04$); median OS with tivozanib was 28.8 months and with sorafenib was 29.3 months.[12] In the Phase III INTORSECT trial, the first randomized controlled trial to compare a VEGF receptor inhibitor against a second-line mTOR inhibitor (in this case after sunitinib), there was no significant difference in the primary end point (PFS) between drugs: 4.28 versus 3.91 months for temsirolimus versus sorafenib, respectively (hazard ratio [HR]: 0.87; $p = 0.193$). However, sorafenib achieved significantly longer survival than temsirolimus: median OS was 16.6 versus 12.3 months (HR: 1.31; $p = 0.01$).[13] Sorafenib was the comparator in several other recent Phase III clinical trials including a first-line trial against the angiopoietin/Tie2 inhibitor AMG 386 achieving a PFS benefit of 9 months,[14] and it was both the second-line comparator[9] and the first-line comparator against axitinib, showing a better OS trend in the first study and a noninferior PFS in the second.[15]

Although large Phase III trials provide invaluable evidence about comparative efficacy and toxicity, patients entered into such studies are selected according to strict criteria. They are generally younger than the wider population with mRCC and have fewer comorbidities.[16–20] Phase III studies in mRCC have generally excluded patients with brain metastases and poor performance status (PS), and those who have a poor prognosis according to standard risk scores[21,22] are under-represented. There is a possibility that such patients excluded from registration studies will have poorer clinical outcomes than those included in clinical trials.[23] It is therefore also important to evaluate agents in expanded-access studies and in everyday clinical practice.[20] Although such studies are less strict than Phase III trials, their findings are a valuable guide to what can be expected when treating patients routinely in a community setting.

The RESET study assessed the efficacy and safety of sorafenib when used to treat patients with mRCC across multiple community-based centers in Italy. Treatment followed prescribing indications and local practice with regard to the management of first- and second-line patients. Its findings should contribute to an understanding of how best to use sorafenib in the context of the agents now available to achieve the greatest benefit for our patients.

Patients & Methods

In this Institutional Review Board (IRB)-approved study, consecutive patients with renal cell carcinoma (RCC) evaluated as stage IV according to the American Joint Committee on Cancer Terms Classification System were identified using institutional databases. Eligible patients were 18 years or older, had a histologic or cytologic diagnosis of predominantly clear cell mRCC, and had not been treated with more than one line of prior targeted agents. Prior adjuvant or neoadjuvant systemic therapy were allowed. To be enrolled in this study treatment with sorafenib had to be initiated between 1 January 2008 through December 2010. Patients had disease at baseline evaluable by computed tomography or MRI, and they had had at least one postbaseline radiologic evaluation. All patients had metastatic disease at the start of treatment with sorafenib. Centers included consecutive eligible patients who began treatment within the enrollment period.

Retrospective data collection from this observational noninterventional study started in 2012, and observations were censored on 31 December 2011, or at the date of the last observation (in the absence of a survival end point). All patients included had therefore been followed for at least 1 year. Patients who had taken part in clinical trials with sorafenib or who were part of the European expanded-access program, those who received sorafenib as third-line therapy or beyond and those for whom no survival data were available were excluded.

The primary end point was OS, defined as the time from first administration of sorafenib to death from any cause. Secondary end points included treatment duration and PFS (defined as the time from start of treatment to disease progression or death from any cause, whichever occurred first; time to tumor assessment was not specified in the protocol). Response rate, also a secondary end point, was calculated on the basis of the best response achieved according to local clinical assessment. Data were also collected on the frequency and grade of adverse events (AEs) using the criteria of the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Kaplan–Meier estimates for OS and PFS are presented. We used the χ^2 test to compare line of therapy, age, number of metastatic sites, comorbidities and risk score. Analyses were performed using SAS software version 9.2 (SAS Institute Inc., NC, USA).

The study was conducted in accordance with the guidelines of the International Conference on Harmonization for Good Clinical Practice and the Declaration of Helsinki, and was IRB approved. Documented approval was obtained from the relevant ethical committees at participating centers and treatment of patient data conformed to Italian laws on privacy.

Results

Patient Characteristics

From February to July 2012, data were collected on 358 patients treated at 37 centers in Italy. Of these enrolled patients, five were excluded from analysis (in three, sorafenib had been third line; two had begun treatment before 2008) leaving 353 patients evaluable for efficacy. All 358 patients enrolled were included in the safety analysis.

shows patients' baseline demographic and clinical characteristics at the start of sorafenib treatment. Overall, 32% of patients

were older than 70 years; 53.8% had some form of comorbidity (39.4% had cardiovascular disease; 11.1% diabetes; 5.7% neurologic or psychiatric disorders; and 5.1% gastrointestinal disease). In relation to their mRCC, 79.6% of patients had more than one site of metastasis, and 8.8% had brain/CNS metastases at the start of treatment with sorafenib. A total of 11% had an Eastern Cooperative Oncology Group (ECOG) PS of 2 or higher; 6.8% were rated as poor risk by the Motzer criteria[21] and 11.6% as poor risk by the Heng score.[22]

Table 1. Baseline demographic and clinical characteristics of evaluable patients at start of sorafenib treatment.

Characteristics	Patients (n = 353)
Male, n (%)	237 (67.14)
Age	
Age (years), mean (range)	64.59 (28–86)
Age ≤70 years, n (%)	240 (68.0)
Age >70 years, n (%)	113 (32.0)
Metastatic sites, n (%)	
≤2	205 (58.07)
3	80 (22.66)
>3	68 (19.26)
Organs involved, n (%)	
Brain and CNS	31 (8.78)
Bone	103 (29.18)
Lung	249 (70.54)
Lymph nodes	151 (42.78)
ECOG PS, n (%)	
0–1	263 (74.50)
≥2	39 (11.05)
NA	51 (14.45)
Heng risk score, n (%) [22]	
Low	32 (9.07)
Intermediate	195 (55.24)
High	41 (11.61)
NA	85 (24.08)
Motzer score, n (%) [21]†	
Low risk	31 (8.78)
Intermediate risk	211 (59.77)
High risk	24 (6.80)
NA	87 (24.65)

†Recalculated using the score components recorded in the patient's case report form.

ECOG PS: Eastern Cooperative Oncology Group performance status; NA: Not available.

Nephrectomy had been performed in 84% of the patients. Overall, 75% had some form of prior systemic therapy (including cytokines and adjuvant or neoadjuvant chemotherapy in 12% of patients). Of the 232 patients who had previously received one or more systemic therapies outside the adjuvant or neoadjuvant settings, 175 (49.5% of the evaluable population) had been treated with sunitinib.

Sorafenib & Subsequent Treatments. In this community-treated population, sorafenib was given as first-line treatment in 157 mRCC patients (44.5%) and second line in 196 (55.5%). Of those patients who received sorafenib as first line, 44 (12.5%) subsequently received sunitinib in second line, and 113 (32.0%) received a treatment other than sunitinib in second line. Most patients receiving sorafenib in second line (173 [49.0%]) received sunitinib as first-line therapy.

Most patients (67.4%) began sorafenib at the recommended starting dose of 800 mg/day; 8.5% started at 600 mg/day and 22.4% at 400 mg/day. Dose reduction was implemented at some stage during treatment in roughly a third of patients (34.8%), and dose interruptions were also necessary in a third of patients (33.7%). Subsequent dose re-escalation was carried out during treatment when appropriate. The dose of sorafenib was increased (if at least one dose change was an increase, in terms of daily dose, compared with the previous dose) in 20.1% of patients. Treating physicians determined individual starting doses according to patient profile and local clinical practice. The median duration of sorafenib treatment overall was 5.0 months. For first-line patients, median duration was 5.5 months and in second-line was 4.6 months. The main reason for sorafenib discontinuation was disease progression (in 51.8% of patients). Only 11.9% discontinued because of a drug-related AE (DRAE). Other reasons for discontinuation included AEs not related to sorafenib (3.1%) or AE relation not specified (0.9%), death (4.0%), patient choice (4.8%) or other/not recorded (0.9%).

After treatment with first-line sorafenib, 73 patients went on to receive a second-line targeted agent: in 60.3% this was sunitinib and in 28.8% everolimus. During the course of the study, new drugs became available that may have influenced subsequent treatment. Twenty-five of the first-line sorafenib patients had a third-line agent (predominantly everolimus), and 11 had a fourth or fifth line of systemic targeted treatment. Of patients for whom sorafenib was second-line therapy, 108 had a third-line agent: in 60.2% of these patients (n = 65), the agent was everolimus, in 11.1% (n = 12) sunitinib, and in 5.6% (n = 6) temsirolimus. In total, 33 patients had a fourth-line agent (predominantly everolimus). Eight patients had five or six lines of treatment.

Efficacy

Overall Survival. A total of 353 patients were evaluable for efficacy. Median OS (95% CI) in the overall population was 17.2 months (15.5–19.6) (Figure 1). As shown in Figure 2A, median OS among patients who received first-line sorafenib was 19.9 months (15.9–25.3). In sorafenib second-line patients median OS (calculated from date of first sorafenib administration) was 16.3 months (13–18.2) (Figure 2B).

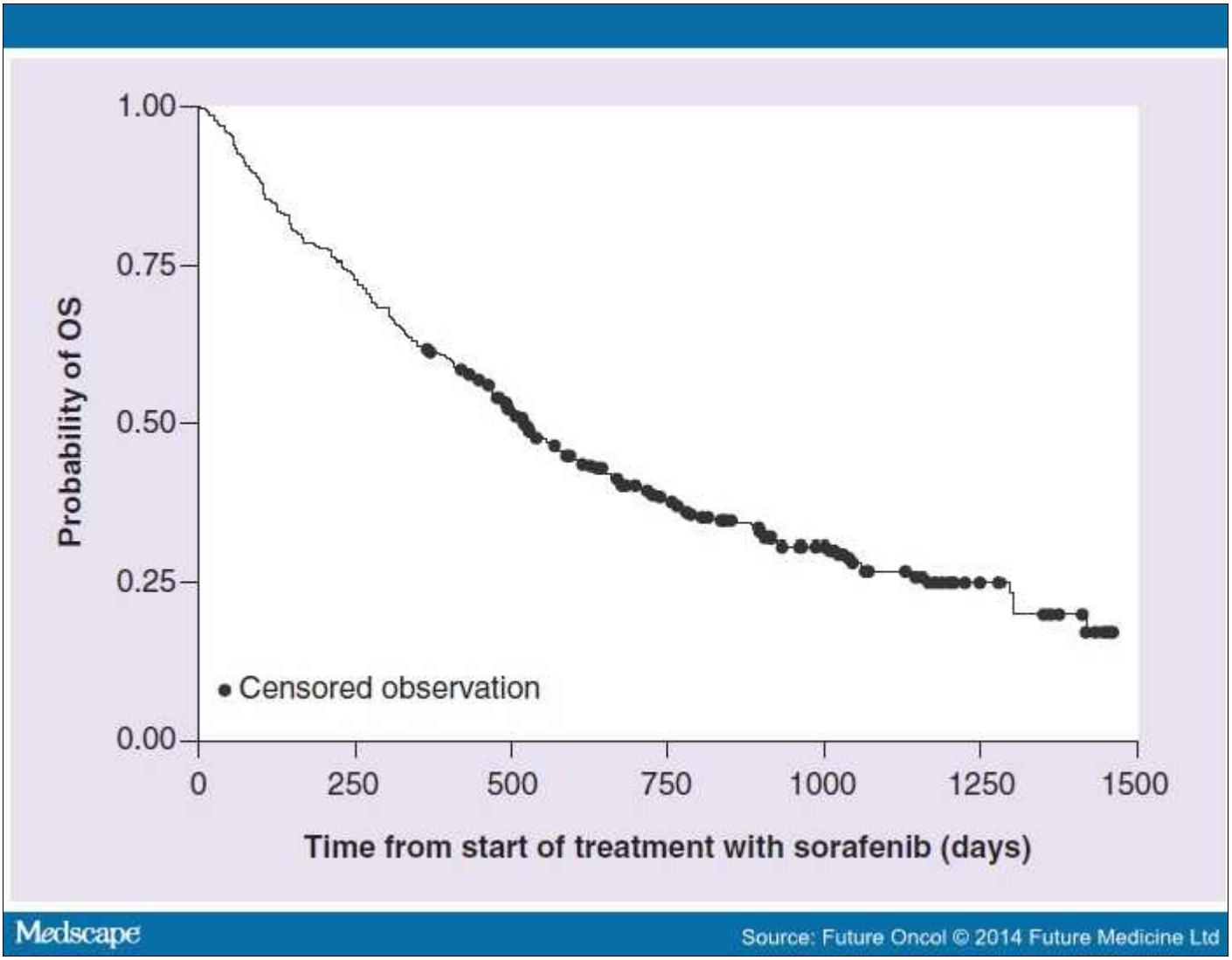

Figure 1.

Overall survival (total population). OS was analyzed in 353 patients evaluable for efficacy: median OS was 17.2 months in the overall population. OS was defined as the time from first administration of sorafenib to death from any cause.

OS: Overall survival.

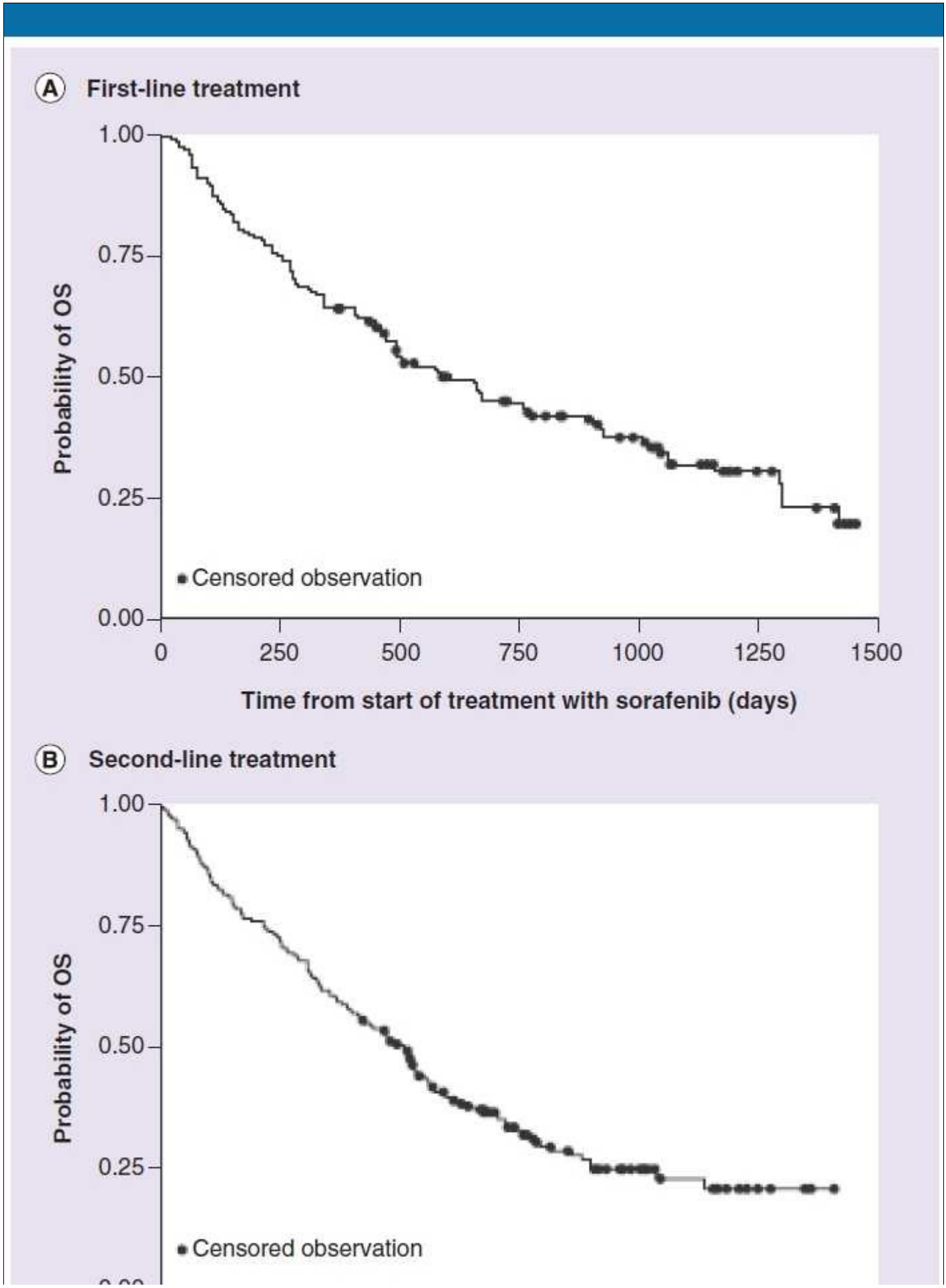
A First-line treatment
Probability of OS
1.00
0.75
0.50
0.25
0.00
Censored observation
0
250
500
750
1000
1250
1500
Time from start of treatment with sorafenib (days)
B Second-line treatment
Probability of OS
1.00
0.75
0.50
0.25
Censored observation

Figure 2.

Stratified overall survival: targeted therapy line of treatment with sorafenib. OS according to sorafenib administration as **(A)** first- or **(B)** second-line treatment. Median OS was 19.9 and 16.3 months, respectively.

OS: Overall survival.

For this community-treated population as a whole, age did not appear to affect survival: median OS (95% CI) was 17.3 months (15.5–19.6) for patients 70 years or younger and 16.1 months (13.9–23.7) for patients older than 70 years (p = 0.96) (Figure 3).

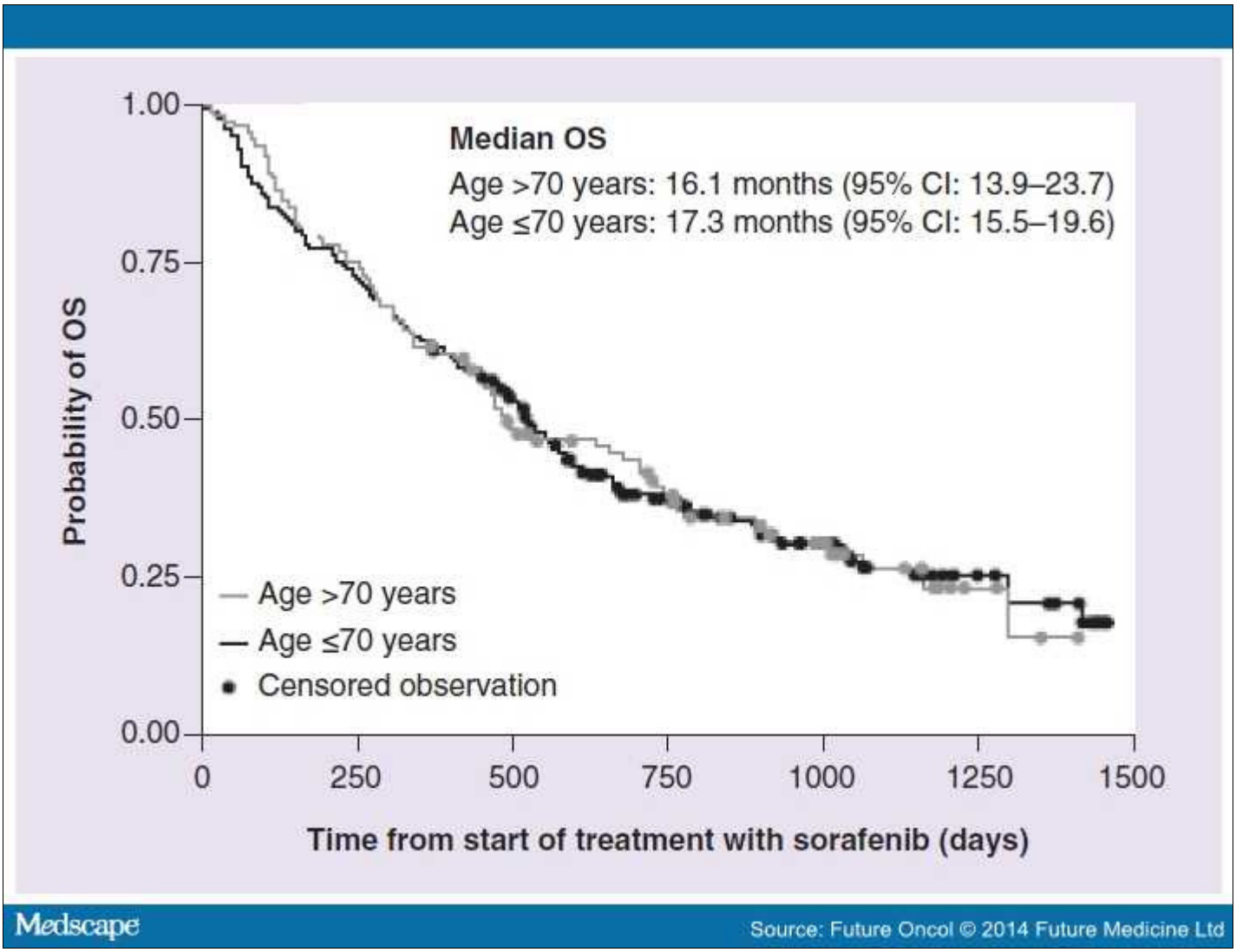

Figure 3.

Stratified overall survival: age at the start of treatment with sorafenib. Considering the treated population, age did not appear to affect survival: median OS (95% CI) was 17.3 months (15.5–19.6) for patients 70 years or younger and 16.1 months (13.9–23.7) for patients older than 70 years (p = 0.96).

OS: Overall survival.

The effect of the number of metastatic sites on prognosis was as expected: median OS for those with two or fewer sites of

involvement was 22.1 months; among patients with three involved sites it was 13.3 months, and in patients with more than three metastatic sides, only 9.7 months (differences between groups: $p < 0.0001$) (Figure 4).

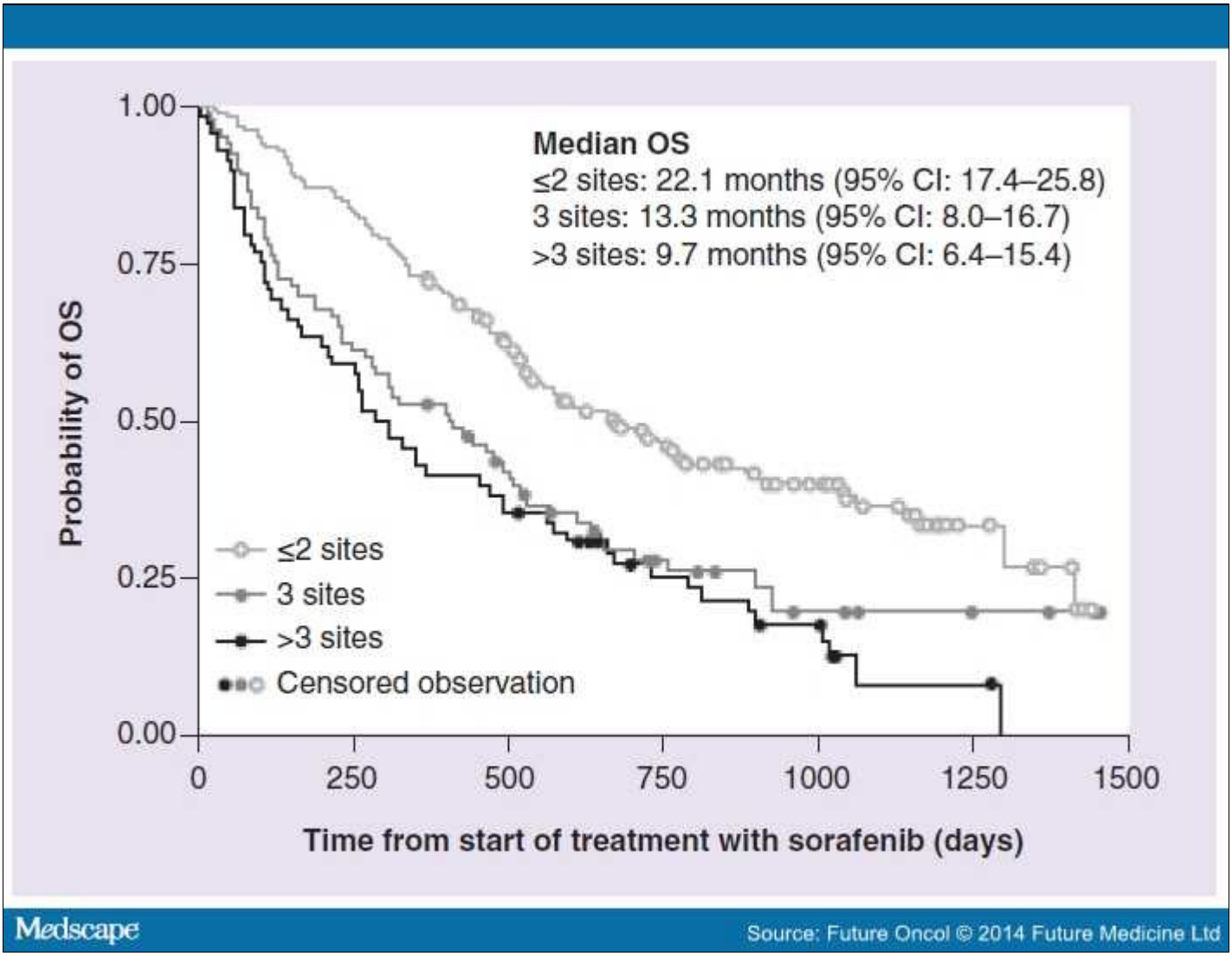

Figure 4.

Stratified overall survival: number of metastatic sites. OS according to extension of disease: median OS of patients with two or fewer metastatic sites, three metastatic sites and more than three metastatic sites was 22.1, 13.3 and 9.7 months, respectively ($p < 0.0001$ for the differences between groups).

OS: Overall survival.

A well-validated prognostic model in RCC and one of the most widely used is the Memorial Sloan–Kettering Cancer Center (Motzer) criteria, which differentiate three risk goups: low, intermediate and high risk of death. By Motzer criteria,[21] patients in the low-risk group had a median OS of 34.3 months, whereas those who were intermediate risk survived a median of 16.7 months and those at high risk only 6.9 months ($p = 0.0001$). By the Heng score, median OS by increasing risk group was 34.8, 17.3 and 7.3 months, respectively. In relation to PS, only patients scoring 0 or 1 were considered for statistical analysis because only a few patients ($n = 39$) had a PS lower than 1. Patients with a PS of 0 ($n = 131$) had a median OS that was significantly longer than those who had a PS of 1 ($n = 132$; 25.8 vs 13.3 months; $p < 0.0001$).

Progression-free Survival. Overall median (95% CI) PFS was 5.9 months (4.9–6.7): 6.6 (4.9–9.3) and 5.3 (4.3–6.0) months in first- and second-line patients, respectively. Low-risk patients by Motzer criteria had a median PFS of 7.7 months, those at

intermediate risk 5.6 months and those at high risk 3.0 months. The median time to first assessment was 2.6 months.

Disease Control. Disease control (complete response plus partial response plus stable disease) was achieved in 55% (n = 195) of patients (). Three patients (0.9%) had a complete response. Of these, in two (1.3%) patients sorafenib was used in first line and in 1 (0.5%) patient it was used in second line. Partial response was obtained in 53(15%) patients overall (20.4% first line and 10.7% second line). Stable disease was observed in 139 (39.4%) patients overall: 36.3% of first-line patients (n = 57) and 41.8% of second-line patients (n = 82).

Table 2. Response rate and duration of response in patients receiving sorafenib as first- or second-line treatment per Response Evaluation Criteria In Solid Tumors (RECIST) version 1.0 criteria.

Response	First-line (n = 157)	Second-line (n = 196)	Total (n = 353)
Complete response, n (%)	2 (1.3)	1 (0.5)	3 (0.9)
Partial response, n (%)	32 (20.4)	21 (10.7)	53 (15.0)
Mean duration of response (months)	7.0	4.3	–
Stable disease, n (%)	57 (36.3)	82 (41.8)	139 (39.4)
Progression disease, n (%)	49 (31.2)	67 (34.2)	116 (32.9)
NA/not recorded, n (%)	17 (10.8)	25 (12.8)	42 (11.9)

NA: Not applicable.

Tolerability

A total of 207 patients (57.8%) experienced at least one DRAE. shows the most frequent events (occurring at any grade in more than 5% of patients). Overall, the most common AE (any grade) was hand–foot skin reaction, followed by diarrhea. However, these events were grade 1–2 in most cases. The most common grade 3 or higher DRAEs were hand–foot skin reaction (6.7% of patients), rash (2.2%), hypertension, fatigue and diarrhea (1.7% each). Alterations in metabolic/laboratory values were rare: aggregating all parameters measured, the total frequency of events was less than 5%; no event was above grade 3.

Table 3. Proportion of patients with at least one adverse event related to sorafenib by description, graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (n = 358).

Adverse event	Grade 1 or 2, n (%)	Grade 3 or 4†, n (%)	Grading NA/not recorded, n (%)
Hand–foot skin reaction	87 (24.3)	24 (6.7)	14 (3.9)
Diarrhea	73 (20.4)	6 (1.7)	3 (0.8)
Mucositis: oral cavity	35 (9.8)	3 (0.8)	4 (1.1)
Fatigue	25 (7.0)	6 (1.7)	4 (1.1)
Rash	21 (5.9)	8 (2.2)	6 (1.7)
Hypertension	19 (5.3)	6 (1.7)	2 (0.6)

†There were no drug-related grade 4 adverse events recorded.

NA: Not applicable.

Among patients younger than 55 years, the DRAE rate was 41.4%. The proportion of patients older than 55 years with at least one AE related to sorafenib was relatively unaffected by age: DRAEs were experienced by 57.3% of patients aged 55–64 years; 63.3% of those 65–74 years and 62.9% of those who were older. Any cardiac AE occurred in 8.1% of patients and was grade 3 or higher in 2.5%.

Discussion

The efficacy and tolerability of sorafenib in clinical trials have been well described. However, patients treated in everyday practice are more heterogeneous than those eligible for registration studies. First data concerning the use of sorafenib with patients very close to real world were reported in two expanded-access studies conducted in North America (NARCCS; n = 2500) and Europe (EUARCCS)[24,25] These studies confirmed patient outcomes achieved in pivotal studies also in patients previously excluded by the TARGET study (e.g., patients with non-clear cell histology, elderly, and metastatic disease of brain or bone).

Sorafenib has now been widely used for more than 7 years. It was approved in Italy in 2006 and reimbursed for patients with advanced mRCC who had failed prior IFN-α- or IL-2-based therapy, or were considered unsuitable for such therapy.[19] However, much still needs to be learned from the systematic reporting of experience in the community setting. The limitations of studies like ours must be acknowledged. It was retrospective and clearly less strict than prospective clinical trials. This was particularly evident in the fact that the time to tumor assessment was not standardized and therefore PFS is a less-reliable measurement of efficacy than OS. Nevertheless, this study contributes valuable insight into the everyday efficacy and safety of sorafenib in Italy.

In several respects, this population differed from that typical for Phase III studies.[23] Patients older than 70 years made up 32% of the population studied in RESET. This contrasts with 13% in the pivotal TARGET trial.[22] Our data (Figure 3) suggest that sorafenib is as effective in terms of OS in patients older than 70 years as it is in younger patients, and it is tolerated similarly well. This supports previous evidence from a subset analysis of the TARGET data showing that outcome was independent of age.[26] Similar data were observed in the two expanded-access studies AARCCS and EUARCCS.[24,25] In the registration TARGET study, patients with brain metastases were excluded.[2] However, in our observational experience with RESET, 8.8% of patients had brain metastases at the start of sorafenib treatment. This proportion is similar to that reported by others in everyday clinical practice and in the expanded-access studies.[24,25,27] The RESET study also included a relatively high proportion of patients who (in relation to controlled trials) were poor risk and had poor PS. Such patients can be expected to have shorter OS.

Among patients treated with second-line sorafenib, the median OS of 16.3 months is very similar to the median OS of 16.6 months found by in the prospective INTORSECT trial.[13] Although the OS data in RESET are from a retrospective analysis, they support the findings of the randomized controlled clinical trial and represent a hard clinical end point. The PFS data in the current study contribute information, but they cannot be seen as reliable as OS because the frequency of tumor evaluation was not standardized across centers.

Sorafenib was recently reported to have a median OS of 29.3 months in the Phase III TIVO-1 trial where most patients (70%) were treatment naive.[12] This is significantly longer than that reported for first-line sorafenib in our study (19.9 months). Although it is difficult to compare data across trials, there are likely differences in patient populations in the Phase III clinical trial population (e.g., 54% ECOG PS 0; 46% ECOG PS 1; 34% low Memorial Sloan–Kettering Cancer Center risk) and our real-world data (74.5% ECOG PS 0–1; 11% ECOG PS 2; 8.8% low risk). The OS data for another Phase III trial (AGILE) are not yet mature.[15]

The extent to which these data contribute to questions about sequencing is uncertain. No nonrandomized evidence will be convincing on this point. However, there is clear interest in the outcome of community-based studies in which agents have been given in different orders. Iacovelli *et al.* [28] recently reported data from a cohort of patients who had received three lines of therapy, suggesting that the sequence of VEGF inhibitor followed by VEGF inhibitor followed by mTOR inhibitor might be associated with better survival than a sequence in which an mTOR inhibitor was sandwiched between two VEGF inhibitors.

AEs were as predicted, given the known safety profile of sorafenib observed in pivotal and expanded-access studies.[27,28] They were manageable and affected only a minority of patients in this community-based study. These data are consistent with those of other studies in which sorafenib was used to treat large and heterogeneous populations of mRCC patients: in the Sorafenib RCC Integrated Database, for example, treatment of more than 4600 patients showed manageable toxicity and no evidence of either new drug-related AEs or cumulative toxicities.[19] Similarly, data from the PREDICT study, which included information on more than 2500 patients (23% of whom were 70 years or older, and 29% with an ECOG PS of 2 or higher) found sorafenib treatment to be well tolerated. Overall, 91% of patients started at the full recommended dose of 400 mg

twice/day; dose reduction was required in only 17%.[17]

Conclusion

This study provides valuable insight into the community management of mRCC in Italy. The efficacy and safety of sorafenib in the first- and second-line settings in everyday clinical practice for treating metastatic mRCC patients were similar to those reported in prospective clinical trials. The median OS of 16.3 months in the second-line setting in this study was similar to the 16.6 months median OS reported in the sorafenib arm of the recent prospective, Phase III INTORSECT trial.

Future Perspective

Patient characteristics (age, comorbidities and life expectations) should help clinicians to identify the best treatment option: patient approach should be validated appropriately, considering that therapeutic indications are often very similar for some drugs. In the present RCC scenario, sorafenib has a large body of evidence in elderly patients. Results of this study are in line with others that indicated sorafenib as the drug of choice for elderly patients.[29,30] Therefore, in the future, it is hoped that the introduction of sorafenib in guidelines for treatment of elderly patients with RCC could become much more than a wishful thinking.

Sidebar

Executive Summary

Background

- Sorafenib is the first tyrosine kinase inhibitor (TKI) approved worldwide for metastatic renal cell carcinoma (mRCC) by the US FDA.
- This Italian retrospective study was performed to assess the efficacy and safety of sorafenib in mRCC patients treated in the community.

Patients & methods

- Patients with histologic or cytologic diagnosis of predominantly clear cell mRCC, not treated with more than one line of prior targeted agents, who received sorafenib between 1 January 2008 and 31 December 2010 were enrolled in our multicenter analysis.

Results

- Data were collected on 358 patients treated at 37 centers in Italy; 353 patients were evaluable for efficacy.
- Median overall survival (OS) in the overall population was 17.2 months; median OS among patients who received first-line sorafenib was 19.9 months. Median OS for second-line sorafenib was 16.3 months.
- Median progression-free survival in the overall population was 5.9 months. It was 6.6 and 5.3 months in first- and second-line sorafenib patients, respectively.
- The most common any-grade drug-related adverse events were hand–foot skin reaction followed by diarrhea.

Conclusion

- The efficacy and safety of sorafenib in first- and second-line settings in everyday clinical practice in the treatment of mRCC patients were similar to those reported in prospective clinical trials.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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