

Clinical outcomes in patients with metastatic renal cell carcinoma receiving everolimus or temsirolimus after sunitinib

Roberto Iacovelli, MD,* Giacomo Carteni, MD,[†] Michele Milella, MD,[§] Rossana Berardi, MD,[‡] Giuseppe Di Lorenzo, MD,[‡] Elena Verzoni, MD,[€] Mimma Rizzo, MD,[†] Matteo Santoni, MD,[‡] Giuseppe Procopio, MD[€]

*Sapienza University of Rome; Department of Radiology, Oncology and Human Pathology, Rome, Italy; [†]Oncology Unit, A. Cardarelli Hospital, Naples, Italy; [§]Medical Oncology A, Regina Elena National Cancer Institute, Rome, Italy; [‡]Department of Medical Oncology, Polytechnic University of the Marche Region, Ancona, Italy; [‡]Medical Oncology, Genitourinary Cancer Section, University Federico II, Naples, Italy; [€]Medical Oncology Unit 1, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Cite as: *Can Urol Assoc J* 2014;8(3-4):e121-5. <http://dx.doi.org/10.5489/cuaj.1604>
Published online March 11, 2014.

Abstract

Introduction: There are little data on the clinical activity of temsirolimus (TM) and everolimus (EV) when used as second-line therapy after sunitinib (SU) in patients with metastatic renal cell carcinoma (mRCC).

Methods: Patients with mRCC treated with EV or TM after SU were included in this retrospective analysis. Progression-free survival (PFS), time to sequence failure (TTSF) from the start of SU to disease progression with EV/TM and overall survival (OS) were estimated using Kaplan-Meier method and compared across groups using the log-rank test. Cox proportional hazards models were applied to investigate predictors of TTSF and OS.

Results: In total, 89 patients (median age 60.0 years) were included. At baseline 43% were classified as MSKCC good-risk, 43% as intermediate-risk and 14% as poor-risk. Median OS was 36.3 months and median TTSF was 17.2 months. Sixty-five patients received SU-EV and 24 patients SU-TM. Median PFS after the second-line treatment was 4.3 months in the EV group and 3.5 months in the TM group ($p = 0.63$). Median TTSF was 17.0 and 18.9 months ($p = 0.32$) and the OS was 35.8 and 38.3 months ($p = 0.73$) with SU-EV and SU-TM, respectively. The prognostic role of initial MSKCC was confirmed by multivariable analysis (hazard ratio 1.76, 95% confidence interval 1.08-2.85. $p = 0.023$).

Conclusions: This study did not show significant differences in terms of disease control and OS between EV and TM in the second-line setting. EV remains the preferred mTOR inhibitor for the treatment of mRCC patients resistant to prior tyrosine kinase inhibitor treatment.

Introduction

Metastatic renal cell carcinoma (mRCC) is the most fatal of all urological cancers, with 5-year survival rates of about 10%.^{1,2} In the past decade the following vascular endothe-

lial growth factor (VEGF)/VEGF receptors (VEGFR) have been developed: sorafenib, sunitinib, pazopanib, axitinib, tivozanib and bevacizumab (in combination with interferon), and 2 mTOR inhibitors have been developed for the treatment of mRCC. Temsirolimus (TM) and everolimus (EV) are currently the only mTOR inhibitors approved by the Food and Drug Administration (FDA) and the European Medical Agency (EMA) for the treatment of mRCC. In contrast to anti-angiogenic agents, mTOR inhibitors act mainly in tumour cells where they inhibit genes related to angiogenesis binding to the immunophilin FK binding protein-12 (FKBP-12); these inhibitors then generate an immunosuppressive complex that inhibits the activation of the mammalian target of rapamycin (mTOR), a key kinase regulatory of cell growth, proliferation, motility, survival as well as in protein synthesis, and transcription.^{3,4} TM is used in the treatment of poor prognosis patients following results of a phase III trial in 626 previously untreated patients with poor prognosis.⁵ Compared with interferon (IFN) and TM plus IFN, TM monotherapy improved overall survival (OS) in patients with mRCC and a poor prognosis.⁵ In another large phase III trial in 410 patients previously pretreated with one or more antiangiogenic agents, randomized to receive EV or placebo, there was a significant increase in progression-free survival (PFS) in patients treated with EV. However, there was no significant improvement in terms of OS, probably because most patients treated in the placebo arm crossed over to the EV arm.⁶ In 2012, Chen and colleagues published a real-world data analysis of 257 patients with mRCC who were receiving second-line EV, sorafenib (SO), or TM after first-line SU. They concluded that the risk of second-line treatment failure after first-line SU was significantly higher with TM and SO compared with EV.⁷

To further investigate the clinical efficacy of these agents, we retrospectively analyzed clinical outcomes in a selected group of patients who received SU as first-line, and EV and TM as second-line therapy.

Methods

Patients

In this retrospective analysis, we reviewed patients with mRCC treated with EV or TM after first-line SU in the main centres involved in kidney cancer treatment in Italy. We only included patients with clear cell histology and measurable disease. For each patient, information on the date of nephrectomy, initial prognostic class based on Memorial Sloan Kettering Cancer Centre (MSKCC) criteria, the type and length of the first-, second- and third-line therapy were collected.⁸ Two sequences of therapy were considered: (1) SU followed by EV (SU-EV) and (2) SU followed by TM (SU-TM).

All patients received SU at a starting dose of 50 mg/day for 4 weeks every 6 weeks. On disease progression, patients were treated with EV (starting dose 10 mg/day orally or TM (starting dose 25 mg intravenously) every week. Patients were treated until disease progression (DP) or an unacceptable level of toxicity. Response assessment by computed tomography (CT) or magnetic resonance imaging (MRI) scans was carried out according to local procedures every 8 to 12 weeks. DP was defined as a $\geq 20\%$ increase of the longer diameter, according to the for RECIST (Response Evaluation Criteria In Solid Tumours) 1.0 criteria.⁹ Values were expressed as median and interquartile range (IQR). PFS was defined as the time from beginning of treatment to DP or to death from any cause, whichever occurred first. Time to sequence failure (TTSF) was defined as the time from the start of SU to the first documentation of DP with EV or TM or to death from any causes, whichever occurred first. OS was defined as the time from start of SU to death or last contact. PFS, TTSF and OS were estimated using Kaplan-Meier method with Rothman's 95% confidence intervals (CI) and compared across groups using the log-rank test. The Chi-Square test was used to assess differences between

groups. Cox proportional hazards models were applied to study patient characteristics as predictors of TTSF and OS in univariate- and multivariable-adjusted analysis using a stepwise selection approach with type I error of 0.05 for model entry and 0.10 for elimination. Additional elimination was applied to identify significant variables at the level of $p < 0.05$, using PASW (Predictive Analytics SoftWare, v. 18, IBM SPSS, Cary, NC).

Results

A total of 89 patients with mRCC were treated with first-line SU followed by EV or TM at 19 Italian centres. An average of 3 patients were treated at each centre and EV was the most used second-line treatment among the available ones in 18 out of 24 centres. The median age was 60.0 years (IQR: 55.4-68.2); 76% of patients were male; 93% had had a radical nephrectomy and 40% were metastatic at diagnosis. The MSKCC prognostic group at the first-line treatment was good in 43%, intermediate in 43% and poor in 14% of patients. Median OS was 36.3 months (95% CI, 31.5-41.0); when stratified by MSKCC classification, this was 70.1 months (95% CI, 33.6-106.5) in the good prognosis group, 36.3 months (95% CI, 30.4-42.1) in the intermediate group and 24.6 months (95% CI, 10.0-39.1) in the poor prognostic group ($p < 0.0001$).

Effects of sequencing with SU-EV or SU-TM

Sixty-five patients received SU-EV and 24 SU-TM and some patients went on to receive third-line therapy with other targeted agents. Median PFS at first line was 11.0 months (95% CI, 8.1-13.9), with no significant differences between the 2 sequencing groups (Table 1).

Median PFS at second line was 4.3 months (95% CI, 3.7-4.8) in patients treated with EV and 3.5 months (95% CI, 3.8-4.5) in those treated with TM; differences were not significant between the 2 groups ($p = 0.63$).

Table 1. Baseline characteristics of patients

| | All patients N=89 | Sequences | | χ^2 test p value |
|-------------------------|-------------------------|-------------------------|-------------------------|--------------------------|
| | | SU-EV n=65 | SU-TM n=24 | |
| Median age (years) | 60.0 (IQR=52.4-68.2) | 60.3 (IQR=55.4-68.3) | 58.2 (IQR=54.6-60.6) | 0.45 |
| Male sex | 76% | 69% | 91% | 0.04 |
| Metastatic at diagnosis | 40% | 43% | 33% | 0.41 |
| MSKCC prognostic group | | | | 0.57 |
| Good | 43% | 48% | 41% | |
| Intermediate | 43% | 46% | 45% | |
| Poor | 14% | 6% | 14% | |
| PFS first line (months) | 11.0 | 11.2 | 8.5 | 0.88* |

SU-EV: sunitinib-everolimus; SU-TM: sunitinib-temsirolimus; IQR: interquartile range; MSKCC: Memorial Sloan Kettering Cancer Center; PFS: progression-free survival; *log-rank test.

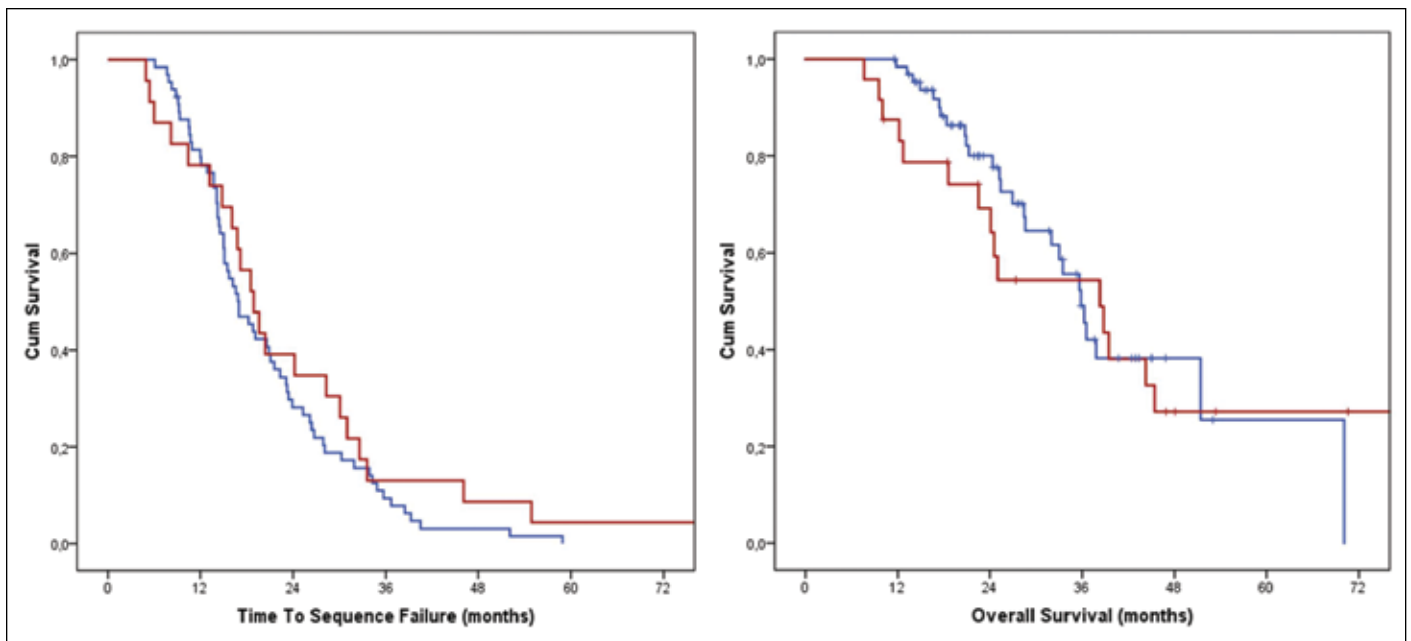


Fig. 1. Time to sequence failure (TTSF) and overall survival (OS) in patients received sunitinib followed by everolimus (blue) or sunitinib followed by temsirolimus (red).

When the 2 sequences were considered, the TTSF was 17.0 (95% CI, 13.8-20.2) and 18.9 (95% CI, 15.1-22.7) months and the OS was 35.8 (95% CI, 32.2-39.4) and 38.3 (95% CI, 18.9-57.7) months for the sequence SU-EV and SU-TM, respectively. No significant differences were found for TTSF ($p = 0.32$) and OS ($p = 0.73$) (Fig. 1).

Partial responses were reported in 13% and 14% of patients treated with EV and TM respectively; stable disease and DP in 47% and 40% of patients who received EV and in 45% and 41% of patients who received TM. There were no significant differences between the 2 groups ($p = 0.99$).

Overall 88% received SO as third-line therapy (86% in the SU-EV and 91% in the SU-TM group) and the remaining patients had a re-challenge with SU or a combination of therapies or were enrolled in clinical trials.

Univariate and multivariable analysis for TTSF and OS

The initial MSKCC prognostic group and the primary resistance to SU were predictive factors on univariate analysis, but their role was not confirmed by multivariable analysis (Table 2).

Moreover, the initial MSKCC prognostic group was an independent prognostic factor in patients treated with EV or TM after SU failure (hazard ratio [HR]: 1.76, 95% CI, 1.08-2.85, $p = 0.023$) (Table 2).

Discussion

EV is a standard therapy in the management of mRCC that has progressed following a tyrosine kinase inhibitor (TKI),

such as SU or SO. The RECORD-1 trial reported a significant increase in PFS (from 1.9 to 4.9 months) with EV compared with placebo, especially in patients treated with first-line SO (5.9 vs. 2.8 months) compared to SU (3.9 versus 1.8 months).¹⁰ In fact, SU was a negative predictive factor for EV activity in the multivariate analysis. Despite this, our data confirm the activity of EV and show a median PFS of 4.3 months and a disease control rate of 60% in a homogeneous group of patients treated with first-line SU. The activity of TM in previously treated patients has been studied in 2 small retrospective studies, with a median PFS ranging from 2.5 to 4.0 months and a clinical response in 90% of patients.^{11,12} In a larger retrospective study MacKenzie and colleagues reported the activity of TM in 87 mRCC patients treated in 3 centres in the United States and Canada.¹³ The study enrolled patients who had progressed after SU (85%) and in intermediate prognostic group. Patients treated with TM showed either a partial response (5%) or stable disease (65%) with median time to progression (TTP) and OS 3.9 and 11.2 months, respectively. Milella and colleagues reported the results of a large prospective phase II trial with TM in patients pre-treated with antiangiogenic agents (43% with SU). Results showed a median PFS of 4.0 months, with a median PFS and OS in those who had previously been treated with SU of 4.6 and 13.7 months, respectively.¹⁴

Similarly to our study, Chen and colleagues evaluated treatment outcomes associated with EV, TM after first-line SU. Patients were followed from the start of second-line treatment until treatment failure (defined as advancement to a third-line therapy or to mortality). The estimated 1-year cumulative probabilities of treatment failure were 49.9%

Table 2. Univariate and multivariable analysis for predictive and prognostic factors in patients treated with everolimus or temsirolimus after sunitinib

| TTSF | Univariate Cox regression | | Multivariable Cox regression | |
|--------------------------------|---------------------------|---------|------------------------------|---------|
| | HR (95% CI) | p value | HR (95% CI) | p value |
| Age | 0.99 (0.97–1.01) | 0.23 | | |
| Sex (F/M) | 0.67 (0.39–1.15) | 0.67 | | |
| First-line MSKCC group | 1.67 (1.16–2.40) | 0.006 | 1.54 (0.91–2.60) | 0.11 |
| Sequence of therapy* | 0.78 (0.48–1.27) | 0.32 | | |
| Primary resistant to sunitinib | 3.02 (1.51–6.06) | 0.002 | 1.73 (0.70–4.30) | 0.24 |
| OS | Univariate Cox regression | | Multivariable Cox regression | |
| | HR (95% CI) | p value | HR (95% CI) | p value |
| Age | 0.96 (0.93–0.99) | 0.030 | 0.96 (0.93–1.00) | 0.057 |
| Sex (F/M) | 0.63 (0.30–1.30) | 0.21 | | |
| First-line MSKCC group | 1.84 (1.12–2.99) | 0.013 | 1.76 (1.08–2.85) | 0.023 |
| Sequence of therapy* | 1.12 (0.59–2.15) | 0.73 | | |
| Primary Resistant to sunitinib | 2.41 (0.97–6.00) | 0.06 | | |

TTSF: time to sequence failure; F: female; M: male; OS: overall survival; HR: hazard ratio; CI: confidence interval; MSKCC: Memorial Sloan Kettering Cancer Centre prognostic classification (good vs. intermediate vs. poor); *sequences are: sunitinib-everolimus compared to sunitinib-temsirolimus.

for EV, 68.4% for SO, and 71.4% for TM. In a multivariate Cox proportional hazards model, a higher adjusted risk of treatment failure versus EV was observed for both TM and SO. The authors concluded that this real-world data analysis suggests that the risk of second-line treatment failure after first-line SU was significantly higher with TM and SO compared with EV; this is in contrast with the results of our study where we found the lack of difference between EV and TM after first-line SU. However, OS in our study was not comparable to our previous experience or with the results of published trials, mainly because our cohort was highly selected in that all patients had clear cell histology, had first-line therapy with SU and were treated with mTORs only as second line. Moreover, patients went on to receive third-line therapy with other targeted agents. As a result of this selection, median OS was about 3 years and up to 6 years in the good prognostic group.

Our study is not without limitations. Its applicability to all patients with mRCC is limited by its retrospective nature, the lack of central radiologic review for the CT scans performed during the treatment, and the difference in the number of patients who received EV and TM. These may affect the overall evaluation of the response and assessment of the PFS. Our results need to be confirmed in prospective randomized trials, but it is important to recall that data on the efficacy of TM have been reported at the European Society for Medical Oncology (ESMO) 2012 conference and the results of the INTORSECT phase III trial (NCT00474786). There were no differences in terms of PFS between TM and SO (4.3 vs. 3.9 months; HR: 0.87, 95% CI, 0.71–1.07; $p = 0.193$), but there was a significant shorter survival in patients treated with TM (12.3 vs. 16.6 months; HR: 1.31, 95% CI, 1.05–1.63; $p = 0.014$).¹⁵

Overall, these results are not conclusive on the role of mTOR inhibitors in the treatment of mRCC. A direct comparison between the activities of TM, EV and SO based on our findings is not possible taking in account our reported limitations. Much debate surrounds the “best” second-line strategy in mRCC, but results to date seem to suggest that the use of TM should be avoided in patients progressed after SU. Finally, this study did not show significant differences in terms of disease control and OS between EV and TM in the second-line setting, where EV remains the preferred mTOR inhibitor for treatment of mRCC patients resistant to prior TKI treatment.

Conclusion

In patients with mRCC who progress on antiangiogenic treatment, EV remains the standard of care if switching to a mTOR inhibitor is the strategy.

This paper has been peer-reviewed.

Competing interests: Dr. Iacovelli serves as a consultant for Bayer and Pfizer and he receives grants for speaking by GSK. Dr. Carteni serves as a consultant for Pfizer, Novartis and GSK. Dr. Di Lorenzo serves as a consultant for Novartis. Dr. Procopio serves as a consultant for Aveo, GSK, Bayer and Pfizer. Dr. Milella, Dr. Berardi, Dr. Verzoni, Dr. Rizzo and Dr. Santoni all declare no competing financial or personal interests.

References

1. Lam JS, Leppert JT, Beldegrun AS, et al. Novel approaches in the therapy of metastatic renal cell carcinoma. *World J Urol* 2005;23:202-12. <http://dx.doi.org/10.1007/s00345-004-0466-0>

2. Garcia JA, Rini BI. Recent progress in the management of advanced renal cell carcinoma. *CA Cancer J Clin* 2007;57:112-25. <http://dx.doi.org/10.3322/canjclin.57.2.112>
3. Sabatini DM. mTOR and cancer: Insights into a complex relationship. *Nat Rev Cancer* 2006;6:729-34. <http://dx.doi.org/10.1038/nrc1974>
4. Thomas GV, Tran C, Mellinghoff IK, et al. Hypoxia-inducible factor determines sensitivity to inhibitors of mTOR in kidney cancer. *Nat Med* 2006;12:122-7. <http://dx.doi.org/10.1038/nm1337>
5. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon-alpha, or both for advanced renal cell carcinoma. *N Eng J Med* 2007;356:2271-81. <http://dx.doi.org/10.1056/NEJMoa066838>
6. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: A double-blind randomized placebo controlled phase III trial. *Lancet* 2008;372:449-56. [http://dx.doi.org/10.1016/S0140-6736\(08\)61039-9](http://dx.doi.org/10.1016/S0140-6736(08)61039-9)
7. Chen CC, Hess GP, Liu Z, et al. Second-line treatment outcomes after first-line sunitinib therapy in metastatic renal cell carcinoma. *Clin Genitourin Cancer* 2012;10:256-61. <http://dx.doi.org/10.1016/j.clgc.2012.04.006>
8. Motzer RJ, Mazumdar M, Bacik J, et al. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. *J Clin Oncol* 1999;17:2530-40.
9. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205-16. <http://dx.doi.org/10.1093/jnci/92.3.205>
10. Motzer RJ, Escudier B, Oudard S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma: Final results and analysis of prognostic factors. *Cancer* 2010;116:4256-65. <http://dx.doi.org/10.1002/cncr.25219>
11. Bojanapally PR, Graham S, Rustine, et al. Temsirolimus for advanced renal cell carcinoma: compassionate versus commercial use. *J Clin Oncol* 2008;26(Suppl):abstr 16139.
12. Schmidinger M, Vogel UM, Lamm W, et al. Temsirolimus in heavily pre-treated patients with metastatic renal cell carcinoma: Preliminary results from the Austrian Compassionate Use Program. *J Clin Oncol* 2008;26(Suppl):abstr 16125.
13. Mackenzie MJ, Rini BI, Elson P, et al. Temsirolimus in VEGF-refractory metastatic renal cell carcinoma. *Ann Oncol* 2011;22:145-8. <http://dx.doi.org/10.1093/annonc/mdq320>
14. Milella M, Di Lorenzo G, Felici A, et al. Medical optimization of Torisel® (MOTOR): A phase II trial of temsirolimus as second-line treatment for advanced RCC by the Italian kidney cancer group (GIR). *Ann Oncol* 2012; 23(Suppl 9):abstract 846P.
15. Hutson T, Escudier B, Esteban E, et al. Temsirolimus vs sorafenib as second line therapy in metastatic renal cell carcinoma: results from the INTORSECT trial. *Ann Oncol* 2012;23(Suppl 9):abstract LBA22 PR.

Correspondence: Dr. Giuseppe Procopio, Medical Oncology Unit 1, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Giuseppe.Procopio@istitutotumori.mi.it