First-line treatment with sunitinib for type 1 and type 2 locally advanced or metastatic papillary renal cell carcinoma: a phase II study (SUPAP) by the French Genitourinary Group (GETUG)†


1Department of Medical Oncology, Bordeaux University Hospital, Bordeaux; 2Department of Medical Oncology, Paris Rene Descartes University, Paris; 3Pathology Department, SCP Pathology, Marseille; 4Department of Medical Oncology, Institut Claudius Regaud/Institut Universitaire du Cancer de Toulouse Oncopole, Toulouse; 5Department of Medical Oncology, Hôpital Foch, Suresnes; 6Research and Development Department, Unicancer, Paris; 7Department of Medical Oncology, Centre Francois Baclesse, Caen; 8Department of Medical Oncology, Centre Eugène Marquis, Rennes; 9Department of Medical Oncology, Institut Claudius Régard/Institut Universitaire du Cancer de Toulouse Oncopole, Toulouse; 10Medic Oncology, Hôpital Saint-Louis, Paris; 11Department of Medical Oncology, Gustave Roussy, Villejuif, France

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Background: Papillary renal cell carcinoma (PRCC), type 1 and type 2, represents 10%–15% of renal cell carcinomas (RCC). There is no standard first-line treatment of metastatic PRCC (mPRCC). Anti-angiogenics have shown activity in...

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Patients and methods: A prospective phase II study evaluated sunitinib in first-line treatment of mPRCC. The primary end point was overall response rate (ORR). Secondary end points were progression-free survival (PFS) and overall survival (OS).

Results: Fifteen and 46 patients, respectively, with type 1 and type 2 mPRCC were enrolled. Using the MSKCC scoring system: 12 (20%), 33 (55%) and 9 (15%) patients were, respectively, in the favourable, intermediate or poor risk group and 7 undetermined. Median follow-up is 51.4 months. In type 1, 2 patients 13% [95% confidence interval (CI) 0.1–30.5] had a partial response (PR), 10 had stable disease (SD) with 5 (33%) ≥12 weeks. In type 2, 5 patients 11% (95% CI 1.9–20.3) had a PR, 25 had SD with 10(22%) ≥12 weeks. Median PFS was 6.6 months (95% CI 2.8–14.8) in type 1 and 5.5 months (95% CI 3.8–7.1) in type 2. Median OS was 17.8 (95% CI 5.7–26.1) and 12.4 (95% CI 8.2–14.3) months, respectively, in type 1 and 2. Safety was as expected with sunitinib for metastatic RCC.

Conclusion: Sunitinib showed activity in treatment of type 1 and 2 mPRCC but lower than in clear-cell mRCC. Both PFS and OS are longer in type I PRCC. Sunitinib represents an acceptable option in first-line treatment of mPRCC.

Key words: renal cell carcinoma, papillary renal cell carcinoma, type 1 papillary renal cell carcinoma, type 2 papillary renal cell carcinoma, anti-angiogenic, sunitinib

introduction

Renal cell carcinoma (RCC) accounts for 3% of all cancers. The most predominant histological subtype form is the clear-cell RCC (ccRCC) which accounts for 75%–80% of patients, while papillary renal cell carcinoma (PRCC) represents 10%–15% of the RCC population. Histologically, PRCC can be separated into two entities with different outcomes. Type 1 contains small cells with a basophilic cytoplasm while type 2 shows large cells with an eosinophilic cytoplasm (Renshaw et al. [1]). PRCC is recognized as an RCC variant with distinct genetic features, characterized primarily by trisomies or tetrasonomies 7 and 17 and loss of chromosome Y, as well as additional gains of chromosomes 3g, 12, 16, and 20 (Kovacs et al. [2]). Hereditary PRCC has been associated with multifocal papillary tumours in type 1 PRCC and hereditary cutaneous and uterine leiomyomas in type 2 PRCC (Zbar et al. [3]). In localized primary tumours, several studies have reported a better outcome for patients with PRCC compared with ccRCC (Amin et al. [4]), and other additional reports showed a better survival for type 1 PRCC versus type 2 (Pignot et al. [5]). However, the survival rate for patients with metastatic PRCC (mPRCC) appears to be worse than ccRCC (Amin et al. [4]; Pignot et al. [5]; Mejean et al. [6]); with the worst prognosis for type 2 PRCC (Mejean et al. [6]).

The outcome for metastatic RCC (mRCC) has been dramatically improved by the discovery of the role of vascular endothelial growth factor (VEGF) in this disease, and the use of anti-VEGF therapy, with the recent approval of five drugs active on the VEGF pathway (Motzer et al. [7], Escudier et al. [8], Hudes et al. [9], Sternberg et al. [10], Escudier et al. [11], [12]). However, most prospective studies have included only, or predominantly, patients with features of ccRCC. Data concerning mPRCC have been mainly drawn from retrospective studies or expanded access programmes in which non-ccRCC population, including predominantly mPRCC, could be enrolled (Dutcher et al. [13], Choueiri et al. [14], Gore et al. [15], Stadler et al. [16]). All these studies reported some partial responses (PRs) with sunitinib without drawing any conclusions as to specific efficacy in the mPRCC setting for any of the drugs available at the time the SUPAP study was designed. Although Von Hippel Lindau abnormalities are not involved in mPRCC, there is some rationale to use anti-VEGF therapy for mPRCC. VEGF expression is increased in PRCC from stage I tumour to stage III–IV, with a significant difference between type 1 and type 2 PRCC (Jacobsen et al. [17]). VEGF 121, VEGFR 1 ARNm and VEGFR 2 ARNm have been shown to be expressed in PRCC tumour samples but lower than in ccRCC (Gunningham et al. [18]).

So far, there is no standard treatment of mPRCC. The SUPAP study was designed to prospectively evaluate the activity of sunitinib in mPRCC.

patients and methods

patients

Key eligible criteria included histologically confirmed, metastatic type 1 or type 2 mPRCC, previously untreated, with measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST 1.0) (Therasse et al. [19]), age ≥18 years, ECOG performance status (PS) ≤1, adequate haematological, renal and hepatic function. Patients were ineligible if they had brain metastases and uncontrolled hypertension (supplementary Appendix S1, available at Annals of Oncology online).

study design

The primary objective of this open-label prospective, non-comparative phase II study was the overall response rate (ORR) by investigator assessment defined as the percent of patients with confirmed complete response (CR) or confirmed PR based on the RECIST criteria, in two independent cohorts defined by the histological type 1 and type 2 mPRCC. Secondary end points were safety of sunitinib in mPRCC patients and time-to-event variables of time to response, duration of response, progression-free survival (PFS), time to disease progression and overall survival (OS).

This study was conducted in accordance with the principles of ethics as stated in the latest version of the Declaration of Helsinki, in Good Clinical Practices and in European Directive 2001/20/CE regarding the conduct of clinical trials. The study was approved by an independent ethics committee (CPP Bordeaux) and the French National Health Authorities (ANSM). The study was registered with Eudract (2006-00339-62) and ClinicalTrials.gov (NCT00541008) databases. All patients gave written informed consent before participating in the trial.
treatment

Sunitinib was administered orally daily at the standard dose of 50 mg for 4 weeks followed by a 2-week rest. All patients received repeated cycles of sunitinib until disease progression, occurrence of unacceptable toxicity, withdrawal of patient consent, or other withdrawal criteria. In case of toxicity, a dose reduction was allowed to 25 mg/day of sunitinib per cycle. Patients were discontinued from the study if the dose level at 25 mg was not tolerated. Patients requiring >4 weeks of dose interruption were discontinued from the study.

assessment of response and toxicity

Tumour assessments were conducted every 12 weeks by the investigator using RECIST 1.0. Toxicity was assessed continuously using Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 [20].

Diagnosis of mPRCC and type 1 or type 2 at inclusion in the study was made according to the local pathological analysis. Any diagnosis of PRCC made outside the investigator’s participating centre had to be confirmed internally by the participating centre or in the reference pathological centre, if solicited. The reference pathological review was done by Dr De Fromont (MF).

statistics

Type 1 and type 2 mPRCC cohorts were designed as two statistically independent phase II studies. A minimum 20% response rate was expected. The study would be negative if the estimated response rate was <5% with a type I error (α) of 0.05. Sunitinib would be accepted as active enough to carry out further studies if the estimated response rate was >20% with a type II error (β) of 0.10. A minimum of 41 assessable patients was necessary in each histological subtype for assessment of the response rate. Taking into account the two-stage design proposed by Simon, the first stage had to include 21 activity assessable patients in each histological type. If one patient or no patients had responded, the cohort would have been stopped and the drug rejected as inactive in that histological subtype. If two or more patients had responded, an additional 20 activity assessable patients had to be included in each tumour type. At the end of the second step, the drug would be rejected as inactive if four or fewer patients responded. If five or more patients responded, the drug would be accepted as active. The response rate was determined by percent and their 95% CIs. Overall and PFSs were estimated by the Kaplan–Meier method.

results

patients

From October 2007 to February 2011, 15 and 47 patients with, respectively, type 1 and type 2 mPRCC were included. One patient included as a type 1 mPRCC but without measurable disease, did not get sunitinib, and therefore was not retained for the analysis. The study went to the second step of the design for type 2 and the type 1 tumour group was closed earlier than planned after only 15 patients due to a low accrual. Baseline characteristics of the enrolled patients are shown in supplementary Table S1, available at Annals of Oncology online. In summary, median age was 64 years old. ECOG PS was 0 in 31 (51%) patients and 1 in 30 patients. Fifty-three (87%) patients had a nephrectomy. Fifty-five (90%) patients had ≥1 metastatic site. Using the MSKCC scoring system (Motzer et al. [21]): 12 (20%), 33 (55%) and 9 (15%) patients, respectively, were in the favourable, intermediate or poor risk group and 7 undetermined. In addition, using the more accurate IDMC scoring system for target therapies and valuable for non-clear-cell RCC population (Kroeger et al. [22]: 15 (25%), 33 (55%) and 13 (20%) patients, respectively, were in the favourable, intermediate or poor risk group). There was a difference in patient characteristics between both mPRCC groups, achieving statistical difference: older patients (69 versus 61 years old), and more lung metastases (86.7% versus 54.3%) in type 1 mPRCC. Among the 61 pathological samples, 49 were reviewed at the participating centre and/or by central review (MF) and 12 did not get a second review (supplementary Table S2, available at Annals of Oncology online). Of the 25 tumour samples that were reviewed both locally and centrally, 21 (84%) were confirmed to be consistent with the initial histological classification mPRCC while 3 were considered to be mPRCC from the other type and 1 was unclassifiable.

activity

All patients but one, who died before the first tumour evaluation from a serious adverse event (SAE) were assessable for activity. Median follow-up was 51.4 months (30.6–57.3). In type 1 mPRCC, 2/15 (13%) patients had a PR, 10 had stable disease (SD) with 5 (33%) ≥12 weeks. In type 2 mPRCC, 5/45 (11%) patients had a PR, 25 had a SD with 10 (22%) ≥12 weeks and 15 a PD (supplementary Table S3, available at Annals of Oncology online). All PR obtained in the type 2 mPRCC group was obtained in the first 41 assessable patients. The primary end point was reached for patients presenting type 2 mPRCC (at least ≥2 PR) and the complete accrual was not achieved in type 1 mPRCC. The median PFS was 6.6 months (95% CI 2.8–14.8) in type 1, and 5.5 months (95% CI 3.8–7.1) in type 2 (supplementary Figure S1, available at Annals of Oncology online). The median OS was 17.8 (95% CI 5.7–26.1) and 12.4 (95% CI 8.2–16) months, respectively, in type 1 and type 2 (supplementary Figure S2, available at Annals of Oncology online).

drug exposure and patient disposition

The median number of cycles was 4 [1–30]. Median dose intensity was 93.3%. Twenty-three patients (38%) required at least one dose reduction to 37.5 mg/day 4 weeks/6 of whom 6 were reduced to 25 mg/day 4 weeks/6. The most common reasons for dose reduction were asthenia (7 patients), hand–foot syndrome (5 patients), diarrhoea (4 patients), mucositis, anorexia and thrombopenia (3 patients each). Supplementary Figure S3, available at Annals of Oncology online, shows the flow of subjects through the trial.

safety

All patients were assessable for toxicity. Toxicity was as previously reported with sunitinib in terms of frequency and severity in RCC. The most frequent and severe side-effects are presented in (supplementary Table S4, available at Annals of Oncology online). One patient died from pulmonary embolism which was considered as possibly related to sunitinib. Sunitinib was suspected in the second occurrence of a non-fatal cardiac infarction in a patient who had not presented any cardiac symptoms since the first episode which had occurred 15 years previously.
This study is the first prospective study of a VEGF targeted agent as only first-line therapy for mPRCC with special focus on type 1 and type 2 separately. Based on the hypothesis to consider the drug efficient if at least 5 objective responses among 41 patients were reported, sunitinib crossed this barrier in type 2 mPRCC, but no formal conclusion can be proposed in type 1 mPRCC due to low accrual. In most studies, both in retrospective and prospective studies, this population is part of a more general patient population depicted as non-clear-cell RCC, although each subtype has its own behaviour, while focusing on mPRCC is warranted. Efficacy of sunitinib was suggested in a retrospective study involving 41 patients (Choueiri et al. [14]). The response rate was low (10%), while PFS was closed to the one reported in ccRCC (8.6 months). Expanded access programmes with sunitinib or sorafenib have also reported efficacy for both drugs (Gore et al. [15]; Stadler et al. [16]). In the expanded access programme using sunitinib, 588 patients with non-clear histology were included but without additional information about sub-group histology (Gore et al. [15]). From this population, 437 patients were reported assessable and among them 48 (11%) had an objective response and 250 (57%) had SD for at least 3 months. On the other hand, one-third of patients progressed within 3 months (Stadler et al. [16]). More recently, four prospective phase II trials in metastatic non-clear-cell carcinoma have been reported (Molina et al. [23], Lee et al. [24], Tannir et al. [25], Tannir et al. [26]). A single-institution phase II trial at the Memorial Sloane Kettering Centre reported activity of sunitinib in 23 patients including 8 mPRCC (Molina et al. [23]). One patient with mPRCC experienced a PR. The median PFS was 5.6 months in the mPRCC population. In a South Korean multicentre study including 22 patients with mPRCC of 31 patients with non-clear-cell histology, 4 patients with mPRCC type 2 of 17 had a PR (Lee et al. [24]). The median PFS was 6.4 months overall with no specific information on mPRCC. Finally, a multi-institutional US phase II study explored sunitinib from naive to third-line treatment in a non-clear-cell presentation (Tannir et al. [25]). Fifty-seven patients were included with 27 patients having mPRCC, predominantly untyped (14 patients) or type 2 (11 patients). No objective response was reported in mPRCC population. The median PFS was 1.6 months in mPRCC and median OS 12.6 months. In a more recent study (ESPN) including patients with non-clear-cell histology, including 27 patients with mPRCC had treatment randomized between sunitinib and everolimus and only 1 patient had a PR with sunitinib. Our study, focused on mPRCC, showed activity in 1st line treatment with a response rate slightly above 10%, much lower than the one obtained in ccRCC. Moreover, the median PFS was also shorter and suggested a shorter PFS in type 2 mPRCC. Furthermore, when considering type 2 mPRCC, there was 30%–35% of patients already with progressive disease at the first evaluation done at 3 months. In this context, it should be added that, in our study, 24% of patients with type 2 mPRCC had liver metastases while no patient in type 1 mPRCC had any liver metastases, which might have had an impact in the outcome as type 2 mPRCC patients with liver metastases in our study had a significant worse PFS than patients without (5.2 versus 5.8 months, \(P = 0.023\)). No specific data regarding the location of metastases between type 1 and type 2 mPRCC and outcome has been reported yet. In addition, there was also a discrepancy with a 16% change in the histological typing of mPRCC mostly between type 1 and type 2. It is therefore recommended that an expert pathological analysis rather than a community analysis be provided and that specific trials in mPRCC be funded.

The side-effect profile of sunitinib was as expected from previous studies in mRCC and did not differ between studies.

Other signalling pathways are considered to be involved in PRCC suggesting that other targeted therapy need to be evaluated. mTOR inhibitors were evaluated in the pivotal phase III study of temsirolimus in first-line treatment of RCC, including all histological types (Hudes et al. [9], Dutcher et al. [13]) and, more recently, two phase II studies with everolimus, one in non-clear-cell histology RCC and one in mPRCC only were reported (Tannir et al. [26], Escudier et al. [27], Koh et al. [28], Voss et al. [29]). In the phase III study, 124 patients with non-clear-cell histology were included in the three-arm trial and 40 patients treated with temsirolimus alone (Hudes et al. [9], Dutcher et al. [13]). In the 37 mPRCC patients treated with temsirolimus alone, the median PFS and OS were similar to ccRCC: 5.9 versus 5.5 and 11.6 versus 10.7 months, respectively (Dutcher et al. [13]). In the final analysis of the RAPTOR study, 92 patients with mPRCC were included and treated with everolimus, while only 71 were centrally confirmed to be mPRCC (Escudier et al. [27]). The median PFS at the central review was 3.7 months (95% CI 2.1–5.7) in type 2 mPRCC and 7.6 months in type 1 mPRCC. Median OS was 21 months (95% CI 15.4–28). The Korean study included non-clear-cell patients and naive as well as post-VEGFR TKI (46.9%) patients (Koh et al. [28]). Of 49 patients, 28 were mPRCC but no information was given regarding naive and post-VEGFR TKI patients. Taking all mPRCC patients, 2 patients had a PR and 14 were stable. No PFS data were provided for naive mPRCC patients. In the more recent retrospective report, 85 naïve or already treated patients with non-clear-cell histology were included for treatment with temsirolimus or everolimus, in which 14 had mPRCC (Voss et al. [29]). Among them 3 patients received mTOR inhibitors longer than 1 year. In the ESPIN study, among 27 patients with mPRCC whom treatment was randomized between sunitinib and everolimus, no patient had an objective response with everolimus (Tannir et al. [26]).

Anti-angiogenics and mTOR inhibitors are the only available drugs that have been prospectively explored in mPRCC with both showing some activity. Only a randomized trial would provide additional information to support one or other drug in 1st line treatment. The ASPEN trial (NCT01108445) is comparing everolimus to sunitinib in the treatment of non-clear mRCC. The inclusion of 108 patients is planned with study completion at the end of 2015. Another study from MD Anderson group is raising the same question with similar design in non-clear RCC population. The question has been partially explored through the randomized phase II trial in naive mRCC patients comparing sunitinib to everolimus followed by a switch at progression (RECORD-3 trial) (Motzer et al. [30]). The first data reported in first-line treatment showed, for the overall population, a significant difference in median PFS at 10.7 months with sunitinib, and 7.8 months with everolimus [HR:
1.43 (1.15–1.77)]. In that population, 66 patients had non-clear-cell histology, without additional information regarding the number and the distribution of mPRCC patients. Of 47 assessable mPRCC patients, median PFS was 7.23 months with sunitinib and 5.09 months with everolimus [HR: 1.54 (0.86–2.75)].

Even more recently, based on the presence of cMET-activating mutations and amplifications in mPRCC, foretinib, a tyrosine kinase inhibitor with a cMET kinase inhibition and inhibition of VEGFR and TIE-2 receptors, has been explored. Patients with mPRCC (retrospective central pathology but no classification on the status of type 1 or 2) were included but stratified for the absence (57 patients) or presence (10 patients) of cMET pathway activation, whatever the mechanism (Choueiri et al. [31]). The median PFS was 9.3 months and median OS not reached. The response rate was correlated with the presence of cMET pathway activation, achieving a 50% response rate compared with 8.7% in the absence of cMET pathway activation. Clearly, foretinib is a promising drug for mPRCC harbouring cMET mutation but, for both subgroup populations, should be compared with anti-angiogenesis and/or mTOR inhibitors. Unfortunately this drug will not be developed further. However, the benefit of cMET inhibition in PRCC needs to be addressed in further studies, with potent drugs such as cabozantinib.

**Conclusion**

Considering mPRCC with no standard treatment and a poor outcome, sunitinib has reached a significant activity in a prospective study for type 2 mPRCC but remains modest and lower than for ccRCC. Outcome of mPRCC appears to be better in type 1 than in type 2 mPRCC. Therefore, outside of clinical trials aimed at identifying more effective treatments in mPRCC, sunitinib remains a therapeutic option.

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Hypertension and angiotensin system inhibitors: impact on outcome in sunitinib-treated patients for metastatic renal cell carcinoma

H. Izzedine1*, L. Derosa2–3, G. Le Teuff4, L. Albiges2 & B. Escudier2

1Department of Nephrology, Monceau Park International Clinic, Paris; 2Department of Medical Oncology, Gustave Roussy, Villejuif, France; 3Department of Medical Oncology, Santa Chiara Hospital, Pisa, Italy; 4Department of Biostatistics and Epidemiology, Gustave Roussy, Villejuif, France

Background: To examine the association between hypertension (HTN), angiotensin system inhibitors (ASI) use and survival outcomes in patients with metastatic renal cell carcinoma (mRCC) treated with sunitinib (SU).

Methods: We retrospectively reviewed all patients with mRCC who received SU as first-line treatment in Gustave Roussy from April 2004 to November 2013. The HTN (either pre-existing or secondary to SU), use of ASI (either before or during SU) were analysed. Overall survival (OS) and progression-free survival (PFS) of different exposures were compared with log-rank test. The associations between exposures and survival outcomes were estimated with hazard ratios (HRs) and 95% confidence interval (CI) through a multivariable Cox model adjusted for age, gender, International mRCC Database Consortium risk group and histology.

Results: Among 213 patients with a 3.6-year median follow-up, 134 were hypertensive and 105 were ASI users with a significant association between the two exposures (P < 0.0001). Hypertensive patients have longer OS (median: 41.6 versus 16.4 months, P < 0.0001) and longer PFS (median: 12.9 versus 5.6 months, P < 0.0001) than non-hypertensive patients (n = 79). ASI users (n = 105) had more HTN_PRE compared with those (n = 108) who did not (65% versus 19%, P < 0.001). Multivariable analysis showed that hypertensive patients were significantly associated with OS (P = 0.05) and marginally with PFS (P = 0.06) while ASI intake was significantly associated with better OS [HR = 0.40; 95% CI (0.24–0.66), P < 0.001] and PFS [HR = 0.55 (0.35–0.86), P = 0.009]. The latter remain statistically significantly associated after controlling for the number of metastases. There is no difference on outcome between patients who receive ASI before starting SU and those who received ASI during SU treatment.

Conclusion: Concomitant use of ASI may significantly improve OS and PFS in mRCC patients receiving SU. HTN is marginally associated with the outcome in these patients.

Key words: metastatic renal cell carcinoma, hypertension, angiotensin system inhibitors, target therapy

*Correspondence to: Dr Hassan Izzedine, Department of Nephrology, Monceau Park International Clinic, 21 rue de Chazelles, 75017 Paris, France. Tel: +33-1-48-88-26-28; Fax: +33-1-48-88-99-88; E-mail: hassan.izzedine@clinique-monceau.com

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