Risk factors of proteinuria in renal cell carcinoma patients treated with VEGF inhibitors: a secondary analysis of pooled clinical trial data

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Background: Proteinuria is a common adverse effect of vascular endothelial growth factor targeted agents, particularly in metastatic renal cell carcinoma (mRCC). However, risk factors for proteinuria are poorly defined.

Methods: Data on 1392 mRCC patients using pazopanib or sunitinib were pooled from two Phase-III clinical trials. Risk factors and prognostic effect of on-therapy proteinuria were evaluated by Cox proportional hazards regression.

Results: Any-grade (1–4) and grade 3/4 proteinuria incidence were 15.0% and 3.7%, respectively. Asian ethnicity, diabetes, baseline systolic blood pressure (SBP), pre-existing grade 1 proteinuria and prior nephrectomy were significant independent predictors of either any-grade or grade 3/4 proteinuria. Proteinuria, particularly grade 3/4 (adjusted hazard ratio 0.53 (95% confidence interval 0.30–0.92)), was associated with improved overall survival.

Conclusions: In mRCC patients using pazopanib or sunitinib, Asian ethnicity, diabetes, SBP, pre-existing proteinuria and prior nephrectomy were independent predictors of on-therapy proteinuria, which was associated with improved survival.
not been specifically studied (Lee et al, 2014; Wang et al, 2014). This study primarily aimed to evaluate risk factors of proteinuria in a large cohort of patients with mRCC treated with either pazopanib or sunitinib.

MATERIALS AND METHODS

Study design and patients. The study was a pooled secondary analysis of patients with mRCC treated in two Phase-III randomised controlled trials: VEG105192 (NCT00334282, n = 435) comparing pazopanib to placebo, and COMPARZ (NCT00720941, n = 1110) comparing pazopanib to sunitinib (Sternberg et al, 2010; Motzer et al, 2013). Anonymised patient level data was remotely accessed via a secure research environment following project approval by an independent review panel of the clinical trial data transparency portal clinicalstudydatarequest.com (reference number: 668; ClinicalTrials.gov Identifier: clinical trial data transparency portal clinicalstudydatarequest.com following project approval by an independent review panel of the level data was remotely accessed via a secure research environment following project approval by an independent review panel of the clinical trial data transparency portal clinicalstudydatarequest.com. The studies were approved by the institutional (reference number: 668; ClinicalTrials.gov Identifier: clinical trial data transparency portal clinicalstudydatarequest.com following project approval by an independent review panel of the clinical trial data transparency portal clinicalstudydatarequest.com. The studies were approved by the institutional review board or ethics committee at each participating centre and all patients provided written informed consent (Sternberg et al, 2010; Motzer et al, 2013).

In brief, the studies enrolled patients who are 18 years or older with mRCC involving a clear-cell histology component; whereas those with baseline grades 2–4 proteinuria (urine protein to creatinine ratio > 0.3 or urine protein dipstick ≥ 1+, and 24-h urine protein > 1 g) among other criteria were excluded (Sternberg et al, 2010; Motzer et al, 2013).

Patient data and outcomes. Baseline covariates evaluated as risk factors for proteinuria were pre-existing grade 1 proteinuria (urine protein to creatinine ratio > 0.3 or urine protein dipstick ≥ 1+, but 24-h urine protein < 1 g), age, sex, ethnicity, body surface area (BSA), baseline systolic blood pressure (SBP), history of diabetes (inferred from baseline use of medicines with ATC code A10A or A10B (Wright et al, 2011)), eGFR (Cockroft-Gault equation), prior nephrectomy, specific VEGF-targeted therapy, use of ASI, use of other antihypertensive drug classes (thiazide-like diuretics, beta-blockers and calcium channel blockers) and use of potentially nephrotoxic drug classes (non-steroidal anti-inflammatory drugs (NSAIDs), bisphosphonates).

The primary outcome evaluated was any-grade of on-therapy proteinuria based on the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0, with grade 3/4 proteinuria (severe/life-threatening) as a secondary outcome. Assessment for proteinuria was generally performed mid-way and at the end of each 6-week cycle of sunitinib/pazopanib therapy.

Statistical analysis. Univariate and multivariable Cox proportional hazards regression was utilised to estimate the association between proteinuria and baseline covariates. Continuous variables were evaluated for non-linearity of association using restricted cubic splines with four knots. Multivariable Cox proportional hazards regression was used to evaluate the prognostic effect of proteinuria on overall survival (OS). The numerical grades of proteinuria (1–4) were included as a time-dependent covariate and was adjusted for pre-existing proteinuria (yes or no), duration of VEGF-targeted therapy, and established prognostic variables of mRCC survival (Heng et al, 2009). In addition, the effect of proteinuria occurring in the first two cycles (12 weeks) of therapy was evaluated.

Multiple imputation by chained equations (n = 20) was applied for analyses involving > 5% overall missing data, otherwise a complete case analysis was reported. All analyses were two-sided and undertaken using the R statistical environment version 3.0.2 (clinicalstudydatarequest.com.).

RESULTS

Baseline characteristics of the 1392 patients pooled from the two clinical studies are displayed in Table 1. On-therapy proteinuria of any-grade was reported for 203 (15%) of patients, with grade 3/4 proteinuria reported for 52 (3.7%) patients. Median time to any-grade and grade 3/4 proteinuria was 32 and 100 days, respectively. Variables included in the analysis had <4% missing data, with the exception of pre-existing proteinuria (10%) and BSA (7%).

Baseline predictors of any-grade proteinuria. In the multivariable analysis, individuals with pre-existing grade 1 proteinuria, Asian ethnicity, and higher SBP had significantly increased risk of any-grade on-therapy proteinuria (Table 2). Prior nephrectomy was associated with reduced risk of any-grade proteinuria. Notably, 30% of participants with an Asian ethnicity had on-therapy proteinuria compared with 8% of participants with white ethnicity (adjusted hazard ratio (HR) of 4.1, P < 0.001). Diabetes, lower BSA and lower eGFR were associated with increased risk of proteinuria in univariate analysis, but were not statistically significant following adjustment for other covariates. Pazopanib had a trend towards increased risk of any-grade proteinuria compared with sunitinib (HR 1.31, P = 0.08).

Baseline predictors of grade 3/4 proteinuria. Pre-existing grade 1 proteinuria, Asian ethnicity and diabetes were identified as significant independent risk factors for on-therapy grade 3/4 proteinuria.

Table 1. Baseline characteristics of the study cohort

| Variable | Mean ± s.d., or n (%) |
|----------|---------------------|
| Pre-existing proteinuria | 221 (18) |
| Age (years) | 60.1 ± 10.8 |
| Male sex | 1005 (72) |
| Ethnicity | 952 (68) |
| White | 414 (30) |
| Asian* | 26 (2) |
| SBP (mm Hg) | 126 ± 13 |
| DBP (mm Hg) | 75 ± 8.9 |
| Heart rate | 78 ± 12 |
| BSA (m²) | 1.91 ± 0.27 |
| Diabetes | 178 (13) |
| eGFR (ml min⁻¹) | 72 ± 26 |
| Prior nephrectomy | 1179 (85) |
| VEGF inhibitor allocated | 844 (61) |
| Pazopanib | 548 (39) |
| Sunitinib | |
| Use of ASI | 350 (26) |
| ACEI | 223 (16) |
| ARB | 135 (10) |
| Use of other AHD | 482 (36) |
| CCB | 270 (20) |
| Beta blocker | 234 (17) |
| Thiazide diuretic | 161 (12) |
| Use of nephrotoxic drug | 342 (25) |
| NSAID | 307 (23) |
| Bisphosphonate | 61 (4) |

Abbreviations: ACEI = angiotensin converting enzyme inhibitor; AHD = antihypertensive drug; ARB = angiotensin receptor blocker; ASI = angiotensin system inhibitor; BSA = body surface area; CCB = calcium channel blocker; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; NSAID = non-steroidal anti-inflammatory drug; SBP = systolic blood pressure; VEGF = vascular endothelial growth factor.

*Predominantly East Asian or Japanese heritage.
Risk factors of proteinuria

Table 2. Association between baseline characteristics and on-therapy any-grade proteinuria

|                        | Unadjusted (univariate) analysis | Adjusted (multivariable) analysis |
|------------------------|---------------------------------|-----------------------------------|
|                        | HR | 95% CI     | P-value | HR | 95% CI     | P-value |
| Pre-existing proteinuria | 3.26 | 1.81–5.87 | <0.001 | 3.04 | 1.65–6.51 | 0.001 |
| Age (per 10 years)      | 1.21 | 0.92–1.58 | 0.173 | 1.16 | 0.82–1.65 | 0.400 |
| Male sex                | 0.99 | 0.53–1.86 | 0.977 | 0.91 | 0.45–1.86 | 0.796 |
| Ethnicity (vs White)    |      |            |        |     |            |        |
| Asian                  | 2.35 | 1.34–4.11 | 0.003 | 3.34 | 1.60–6.95 | 0.001 |
| Other                  | 1.61 | 0.22–12.0 | 0.641 | 1.38 | 0.18–10.4 | 0.758 |
| SBP (per 10 mm Hg)      | 1.22 | 0.99–1.50 | 0.065 | 1.14 | 0.91–1.43 | 0.267 |
| BSA (per m²)           | 0.51 | 0.18–1.46 | 0.210 | 0.57 | 0.12–2.67 | 0.477 |
| Diabetes               | 3.24 | 1.78–5.91 | <0.001 | 2.04 | 1.03–4.00 | 0.040 |
| eGFR (per 10 ml min⁻¹) | 1.00 | 0.91–1.11 | 0.957 | 1.07 | 0.93–1.22 | 0.349 |
| Prior nephrectomy      | 0.67 | 0.34–1.34 | 0.256 | 0.81 | 0.38–1.72 | 0.588 |
| Pazopanib (vs sunitinib) | 1.02 | 0.57–1.83 | 0.942 | 0.98 | 0.54–1.79 | 0.950 |
| Use of ASI             | 1.71 | 0.98–2.99 | 0.061 | 1.48 | 0.75–2.91 | 0.256 |
| Use of other AHD       | 1.85 | 1.06–3.21 | 0.030 | 1.35 | 0.70–2.60 | 0.367 |
| Use of nephotoxic drug  | 1.57 | 0.88–2.81 | 0.128 | 1.53 | 0.81–2.89 | 0.188 |

Abbreviations: AHD = antihypertensive drug, ASI = angiotensin system inhibitor, BSA = body surface area, CI = confidence interval, eGFR = estimated glomerular filtration rate; HR = hazard ratio; SBP = systolic blood pressure. Note: multiple imputation estimates reported for unadjusted pre-existing proteinuria and BSA, and all adjusted covariates.

Table 3. Association between baseline characteristics and on-therapy grade 3/4 proteinuria

|                        | Unadjusted (univariate) analysis | Adjusted (multivariable) analysis |
|------------------------|---------------------------------|-----------------------------------|
|                        | HR | 95% CI     | P-value | HR | 95% CI     | P-value |
| Pre-existing proteinuria | 3.04 | 1.88–5.17 | <0.001 | 3.04 | 1.65–6.51 | 0.001 |
| Age (per 10 years)      | 1.03 | 0.90–1.17 | 0.675 | 1.03 | 0.87–1.22 | 0.711 |
| Male sex                | 1.09 | 0.79–1.50 | 0.600 | 1.07 | 0.75–1.54 | 0.702 |
| Ethnicity (vs White)    |      |            |        |     |            |        |
| Asian                  | 4.13 | 3.08–5.54 | <0.001 | 4.12 | 2.86–6.93 | <0.001 |
| Other                  | 1.53 | 0.48–4.86 | 0.471 | 1.45 | 0.45–4.63 | 0.535 |
| SBP (per 10 mm Hg)      | 1.06 | 0.96–1.18 | 0.272 | 1.14 | 1.02–1.28 | 0.025 |
| BSA (per m²)           | 0.23 | 0.13–0.40 | <0.001 | 0.75 | 0.33–1.74 | 0.507 |
| Diabetes               | 1.62 | 1.13–2.31 | 0.009 | 1.45 | 0.98–2.14 | 0.067 |
| eGFR (per 10 ml min⁻¹) | 0.94 | 0.89–0.99 | 0.031 | 0.97 | 0.89–1.04 | 0.372 |
| Prior nephrectomy      | 0.71 | 0.50–1.01 | 0.060 | 0.67 | 0.46–0.98 | 0.040 |
| Pazopanib (vs sunitinib) | 1.31 | 0.97–1.78 | 0.075 | 1.28 | 0.94–1.74 | 0.112 |
| Use of ASI             | 0.80 | 0.57–1.11 | 0.180 | 1.03 | 0.70–1.50 | 0.897 |
| Use of other AHD       | 0.92 | 0.69–1.23 | 0.578 | 0.97 | 0.69–1.36 | 0.869 |
| Use of nephotoxic drug  | 0.74 | 0.52–1.05 | 0.091 | 0.93 | 0.64–1.34 | 0.687 |

Abbreviations: AHD = antihypertensive drug, ASI = angiotensin system inhibitor, BSA = body surface area, CI = confidence interval, eGFR = estimated glomerular filtration rate; HR = hazard ratio; SBP = systolic blood pressure. Note: multiple imputation estimates reported for unadjusted pre-existing proteinuria and BSA, and all adjusted covariates.

proteinuria (Table 3). Individuals with pre-existing grade 1 proteinuria had an 8.1% risk of grade 3/4 proteinuria, compared with 2.7% for individuals without pre-existing proteinuria (adjusted HR of 3.04, P = 0.001). Individuals with Asian ethnicity had a 6.5% risk of grade 3/4 proteinuria compared with 2.5% risk for individuals with white ethnicity (adjusted HR of 3.34, P = 0.001). Individuals with diabetes had a 9.0% risk of grade 3/4 proteinuria (Table 3). Furthermore, dose modification due to proteinuria was more common for Asian participants than White participants (P = 0.001, Supplementary Table 1).

Association between proteinuria and overall survival. Over a median follow-up of 30 months, 690 (50%) deaths were recorded. There was a statistically significant association between grade of proteinuria and OS (adjusted HR of 0.86 for each increase in grade, P = 0.015). Notably, the adjusted OS HR was 0.53 (95% CI 0.30–0.92) for grade 3/4 proteinuria compared with no on-therapy proteinuria. Early proteinuria (first 12 weeks of therapy) had a trend towards association with improved OS (adjusted HR of 0.86 for each increase in grade, P = 0.053). Median OS was 27.8 and 33.1 months, and was not reached within the study.
period, for patients without proteinuria in the first 12 weeks; those with grade 1/2 proteinuria in the first 12 weeks; and those with grade 3/4 proteinuria in the first 12 weeks, respectively (Supplementary Figure 1).

DISCUSSION

This study is the first to evaluate in detail the difference between Asian and White patients with respect to the risk of proteinuria during VEGF-targeted therapy. Clinical studies of Asian populations have raised the possibility that adverse event profiles may differ between Asian and non-Asian populations (Lee et al, 2012). The largest prior study included 169 patients with mRCC. There was no evidence to indicate that baseline use of ASIs, other antihypertensive drugs, NSAIDs and bisphosphonates significantly altered the risk of proteinuria. Proteinuria was also observed to be a potential biomarker of improved survival following use of VEGF-targeted agents.

REFERENCES

Feliu J, Salah A, Safont MJ, Garcia-Giron C, Aparicio J, Losa F, Bosch C, Escudero P, Casado E, Jorge M, Bohn U, Perez-Carrion R, Carmona A, Custodio AB, Maurel J (2015) Correlation of hypertension and proteinuria with outcome in elderly bevacizumab-treated patients with metastatic colorectal cancer. PLoS One 10: e0116527.

Gross JL, de Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T (2005) Diabetic nephropathy: diagnosis, prevention, and treatment. Diabetes Care 28: 164–176.

Heng DYC, Xie W, Regan MM, Warren MA, Golshayan AR, Sahi C, Egi1 BJ, Ruether JD, Cheng T, North S, Venner P, Knox JJ, Chi KN, Kolmannsberger C, McDermott DF, Oh WK, Atkins MB, Bukowski RM, Rini BI, Choueiri TK (2009) Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor–targeted agents: results from a large, multicenter study. J Clin Oncol 27: 5794–5799.

Horsley L, Marti K, Jayson GC (2012) Is the toxicity of anti-angiogenic drugs predictive of outcome? A review of hypertension and proteinuria as biomarkers of response to anti-angiogenic therapy. Expert Opin Drug Metab Toxicol 8: 283–293.

Izdeined H, Massard C, Sano JP, Goldwasser F, Khayat D, Soria JC (2010) VEGF signalling inhibition-induced proteinuria: Mechanisms, significance and management. Eur J Cancer 46: 439–448.

Izdeined H, Soria JC, Escudier B (2013) Proteinuria and VEGF-targeted therapies: an underestimated toxicity? J Nephrol 26: 807–810.

Kim HR, Park HS, Kwon WS, Lee JH, Tanigawara Y, Lim SM, Kim HS, Shin SJ, Ahn JB, Rha SY (2013) Pharmacogenetic determinants associated with sunitinib-induced toxicity and ethnic difference in Korean metastatic renal cell carcinoma patients. Cancer Chemother Pharmacol 72: 825–835.

Lee S-H, Bang Y-J, Mainwaring P, Ng C, Chang JWC, Kwong P, Li RK, Suriapong V, Toh C-K, Yuan J, Pitman Lownenthal S, Chung HC (2014) Sunitinib in metastatic renal cell carcinoma: an ethnic Asian subpopulation analysis for safety and efficacy. Asia Pac J Clin Oncol 10: 237–245.

Miller KD, Chap LI, Holmes FA, Cobleigh MA, Marcom PK, Fehrenbacher L, Dickler M, Overmoyer BA, Reimann JD, Sing AP, Langmuir V, Rugo HS (2005) Randomized phase III trial of capcitabine compared with sunitinib or pazopanib in patients with previously treated metastatic breast cancer. J Clin Oncol 23: 792–799.

Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, Nathan P, Staelher M, de Souza P, Merchant JR, Boleti E, Fife K, Jin J, Jones R, Uemura H, De Giorgi U, Harmenberg U, Wang J, Sternberg CN, Deen K, McCann L, Hackshaw MD, Crescenzo R, Pandite LN, Choueiri TK (2013) Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med 369: 722–731.

Nangia CS, Wang D, Scarpace L, Schultz L, Khanshour A, Mikkelsen T (2011) The role of the development of hypertension or proteinuria in predicting outcome with the use of bevacizumab for patients with glioblastoma multiforme (GBM). ASCO Meeting Abstracts e2021.

Conflict of Interest

The authors declare no conflict of interest.
Ramirez SP, Mcclellan W, Port FK, Hsu SI (2002) Risk factors for proteinuria in a large, multiracial, southeast Asian population. J Am Soc Nephrol 13: 1907–1917.

Sternberg CN, Davis ID, Mardiak J, Szczyluk C, Lee E, Wagstaff J, Barrios CH, Salman P, Gladkov OA, Kavina A, Zarbaj JJ, Chen M, McCann L, Pandite L, Roychowdhury DF, Hawkins RE (2010) Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol 28: 1061–1068.

Tomita Y, Uemura H, Fujimoto H, Kanayama H-o, Shinohara N, Nakazawa H, Imai K, Umeyama Y, Ozono S, Naito S, Akaza H (2011) Key predictive factors of axitinib (AG-013736)-induced proteinuria and efficacy: A phase II study in Japanese patients with cytokine-refractory metastatic renal cell Carcinoma. Eur J Cancer 47: 2592–2602.

Wang Y, Choueiri TK, Lee JL, Tan MH, Rha SY, North SA, Kollmannsberger CK, McDermott DF, Heng DYC (2014) Anti-VEGF therapy in mRCC: differences between Asian and non-Asian patients. Br J Cancer 110: 1433–1437.

Zemaitis P, Liu K, Jacobs Jr DR, Cushman M, Durazo-Arvizu R, Shoah M, Palmas W, Cooper R, Kramer H (2014) Cumulative systolic BP and changes in urine albumin-to-creatinine ratios in nondiabetic participants of the multi-ethnic study of atherosclerosis. Clin J Am Soc Nephrol 9: 1922–1929.

Zhang Z-F, Wang T, Liu L-H, Guo H-Q (2014) Risks of proteinuria associated with vascular endothelial growth factor receptor tyrosine kinase inhibitors in cancer patients: a systematic review and meta-analysis. PLoS One 9: e90135.

Zhu X, Wu S, Dahut WL, Parikh CR (2007) Risks of proteinuria and hypertension with bevacizumab, an antibody against vascular endothelial growth factor: systematic review and meta-analysis. Am J Kidney Dis 49: 186–193.

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