SHORT COMMUNICATION

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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.

Anti-angiogenic agents targeting the vascular endothelial growth factor (VEGF) pathway have demonstrated efficacy for the treatment of a range of cancers, including metastatic renal cell carcinoma (mRCC). Proteinuria is a relatively common adverse effect of VEGF-targeted agents, particularly in mRCC (Zhu *et al*, 2007; Wu *et al*, 2010; Zhang *et al*, 2014), and its pathogenesis is likely multifactorial (Izzedine *et al*, 2013). It has been suggested that proteinuria may be a biomarker of clinical response to VEGF-targeted agents, but the evidence is currently inconclusive (Horsley *et al*, 2012).

Although risk factors for proteinuria in the general population (e.g., diabetes and hypertension) are well studied (Ramirez *et al*, 2002; Gross *et al*, 2005), they are poorly defined following use of VEGF-targeted agents (Izzedine *et al*, 2010). A few small studies have identified baseline urine protein, estimated glomerular filtration rate (eGFR), diabetes and use of pamidronate as potential risk factors of proteinuria with VEGF-targeted therapy (Miller *et al*, 2005; Tomita *et al*, 2011; Feliu *et al*, 2015). In chronic kidney disease, the use of angiotensin system inhibitors (ASIs), angiotensin converting enzyme inhibitors or angiotensin receptor blockers has been shown to reduce the risk and progression of proteinuria. However, it is unknown whether use of ASIs may reduce the risk of proteinuria associated with VEGF-targeted therapies. Moreover, adverse event profiles for VEGF-targeted therapy appear to differ between Asian and non-Asian populations, although differences with respect to proteinuria have

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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: NCT02156310). 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 enroled 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 $\geqslant 1+$, 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 $\geqslant 1+$, 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

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	
White	952 (68)
Asian[a]	414 (30)
Other	26 (2)
SBP (mm Hg)	126 ± 13
DBP (mm Hg)	75 ± 8.9
Heart rate	78 ± 12
BSA (m^2)	1.91 ± 0.27
Diabetes	178 (13)
eGFR (ml min^{-1})	72 ± 26
Prior nephrectomy	1179 (85)
VEGF inhibitor allocated	
Pazopanib	844 (61)
Sunitinib	548 (39)
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.
[a]Predominantly East Asian or Japanese heritage.

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	1.68	1.20–2.34	0.003	1.65	1.17–2.33	0.005
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	2.86–5.93	<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 m^2)	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 nephrotoxic 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.

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	3.26	1.81–5.87	<0.001	3.04	1.65–5.61	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 m^2)	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 nephrotoxic 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.

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 compared with 3.0% for individuals without diabetes (adjusted HR of 2.04, $P = 0.04$). Use of non-ASI antihypertensive drugs was marginally statistically significant in univariate analysis, but not following adjustment for other covariates. No significant difference in risk of grade 3/4 proteinuria was observed between pazopanib and sunitinib.

Dose modifications amongst Asian and White participants. Exploratory analysis indicated that Asian participants in the COMPARZ study were more likely to have a dose modification (interruption or reduction) than White participants ($P = 0.018$, Supplementary Table 1). 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*, 2014; Wang *et al*, 2014), but differences in proteinuria have not been studied specifically. It has been hypothesised that differences in BSA (particularly the smaller BSA in Asians) may partially explain these differences in trial adverse events (Zhou, 2012; Lee *et al*, 2014). In the current study, we observed that the risk of any-grade and grade 3/4 proteinuria is increased for Asian patients, and that this difference is not explained by any of the other covariates assessed—including BSA. It has been speculated that differences in adverse events between Asian and non-Asian populations may be due to genetic differences (Kim *et al*, 2013).

This study also highlights that diabetes is independently associated with significantly higher incidence of on-therapy grade 3/4 proteinuria. This is concordant with a study of 127 patients using bevacizumab for metastatic colorectal cancer (Feliu *et al*, 2015), and the well-established association between diabetes and proteinuria in the general population (Gross *et al*, 2005). SBP, a well-established risk factor for proteinuria and renal disease in the general population (Ramirez *et al*, 2002; Zemaitis *et al*, 2014), was also observed to be associated with increased risk of on-therapy proteinuria.

In addition, individuals with pre-existing grade 1 proteinuria were at significantly higher risk of any-grade and grade 3/4 proteinuria which is concordant with results from a small study of Japanese patients using axitinib for mRCC (Tomita *et al*, 2011). In contrast to a prior study (Tomita *et al*, 2011), we did not find a significant association between baseline eGFR and on-therapy proteinuria. Although a significant unadjusted association between eGFR and any-grade proteinuria was observed, this was not significant following adjustment for other covariates.

There was no evidence that use of an ASI significantly reduced the risk of proteinuria following commencement of sunitinib/pazopanib, or that use of NSAID or bisphosphonate drugs significantly increased the risk. The results of the current study were discordant with a prior study reporting that use of pamidronate (a bisphosphate drug) was associated with increased risk of proteinuria with bevacizumab treatment of metastatic breast cancer (Miller *et al*, 2005). The effects of ASIs and NSAIDs on proteinuria associated with VEGF-targeted therapy have not been previously reported. It is possible that the relationship is confounded by unmeasured variables that effect both the use of these medicines and the risk of proteinuria.

Proteinuria following commencement of sunitinib/pazopanib was associated with significantly improved OS. Specifically, the higher the grade of on-therapy proteinuria the better the survival outcome. Although this association has been studied previously, these studies have been limited by much smaller sample sizes (Horsley *et al*, 2012). The largest prior study included 169 patients with glioblastoma multiforme treated with bevacizumab and reported that proteinuria was independently associated with improved survival (Nangia *et al*, 2011). The second largest prior study included 127 patients with metastatic colorectal cancer treated with bevacizumab and found a significant association with improved response rate, but not OS (Feliu *et al*, 2015). This association requires further validation, but it is possible that proteinuria is highlighting individuals with greater exposure or sensitivity to pazopanib/sunitinib A potential limitation of using proteinuria as a biomarker is that grade 3/4 proteinuria often occurs relatively late after starting therapy (median time to onset of 100 days).

In conclusion, Asian ethnicity, diabetes, baseline SBP, pre-existing proteinuria and prior nephrectomy were predictors of proteinuria during sunitinib or pazopanib therapy for 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.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies this paper on British Journal of Cancer website (http://www.nature.com/bjc)