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VEGF signalling inhibition-induced proteinuria: Mechanisms, significance and management

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ABSTRACT

Proteinuria is a dose-related side-effect occurring after inhibition of vascular endothelial growth factor (VEGF) signalling and may reflect severe glomerular damage. The inhibition of the VEGF signalling axis induces downexpression or suppression of nephrin, an important protein for the maintenance of the glomerular slit diaphragm, sometimes leading to nephritic syndrome and/or glomerular thrombotic microangiopathy, the main-associated kidney disease. A MEDLINE search was carried out using the following criteria: (1) all MEDLINE listings as of 01-01-2000 with abstracts; (2) English language; and (3) Humans. The following phrases were used to query the database: (proteinuria) AND (anti-VEGF OR VEGF inhibition OR bevacizumab OR sunitinib OR sorafenib OR VEGF Trap OR axitinib OR pazopanib OR AZ 2171). The references of each article identified were carefully reviewed for additional reference. The incidence of mild and asymptomatic proteinuria ranges from 21% up to 63%, but heavy proteinuria has been reported in up to 6.5% of renal cell carcinoma patients. Although discontinuation of anti-VEGF agent induced significant reduction, persistence of proteinuria is common. Although angiotensinconverting-enzyme inhibitors and/or angiotensin receptor blockers seem to be preferred, no specific recommendation for an antiproteinuric agent can be made in this context because there are no controlled studies addressing the subject. Periodic monitoring of urinary protein should be carried out in anti-VEGF-treated patients and patients showing proteinuria need special referral to nephrologists.

1. Introduction

Proteinuria and/or hypertension are shared toxic effects among all therapies targeting the vascular endothelial growth factor (VEGF) pathway. Proteinuria can be a major clue to underlying renal disease or a transient finding in those patients. The onset of urinary protein excretion is of importance because proteinuria is a prognostic marker and an independent risk factor for cardiovascular disease.[1] Whether the development of proteinuria might also serve as a surrogate marker of on-target effect (antitumour efficacy) and/or off-target effect (adverse event) is unknown. This article will deal

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with the evaluation of a treated-patient with proteinuria, what basic investigations are needed and when to refer to a nephrologist.

2. Proteinuria: physiology, detection and clinical evaluation

The term proteinuria is taken to mean abnormally high protein excretion in the urine. Proteinuria is the consequence of glomerular filtration of plasma proteins, their defective subsequent reabsorption by the proximal tubular cells and secretion by the tubular cells and distal urinary tract. In humans, close to 180 l of primary urine are produced each day at capillary pressures. Only 5 mg of proteins pass across the glomerular barrier per litre of primitive urine, this is about 900 mg a day. Up to 98% of these are reabsorbed in the proximal tubule. There is a further source of protein secretion from the distal loop of Henle (Tamm–Horsfall protein). Finally, urinary protein excretion in a normal adult should be less than 150 mg/day or 60 mg/m^2/day. Proteinuria is said to be present when the urine contains more than 300 mg protein per day (or 200 mg/l). Therefore, the quantitative and qualitative evaluation of proteinuria is important for the diagnosis of renal disease. Urine with daily protein excretion of 30–300 mg and superior to 300 mg reflects micro and macroalbuminuria, respectively (Available at: http://www.emedicine.com/ped/topic3048.htm. Accessed November 27, 2008).

There are several qualitative and quantitative tests available for the measurement of urinary protein. A urinalysis dipstick is quite sensitive for albuminuria but is insensitive to the presence of non-albumin proteins. Thus pure tubular proteinuria will not be diagnosed unless a 24-h urine sample is collected. A positive dipstick (only when protein excretion exceeds 300 mg/day) usually reflects glomerular proteinuria. They are intended to correlate as follows: + with 0.3 g/l, ++ with 1 g/l, +++ with 3 g/l and ++++ with >3 g/l. False-positive results may be obtained with concentrated or alkaline urine and with many iodinated radiocontrast agents.[2] False-negative results may be obtained with dilute or markedly acidic urine. On the other hand, there are a variety of semiquantitative dipsticks which can be used to screen for albuminuria, including microalbuminuria. Whenever proteinuria is suspected, a urine sample should be sent for laboratory quantification. The gold standard in adults is a 24-h collection so that protein excretion may be expressed per unit body surface area per day (mg/m^2/day). Timed urine collections are not always practical, particularly in old patients or those with deteriorating general conditions. Many clinicians prefer to use albumin excretion in relation to that of creatinine to correct for differences in urine dilution. Normally, the albumin-creatinine concentration ratio is <30 μg/mg.[3,4] There are three basic types of proteinuria: glomerular, tubular and overflow.[5] All three types are easily separated by urine protein electrophoresis. Glomerular proteinuria is due to increased filtration of macromolecules (such as albumin, molecular weight 69,000) across the glomerular capillary wall and is identified on a urine dipstick. Tubular proteinuria or low molecular weight proteins, such as ß2-microglobulin, immunoglobulin light chains, retinol-binding protein, and amino acids, can be filtered across the glomerulus and are then almost completely reabsorbed in the proximal tubule. Tubular proteinuria is often not diagnosed clinically since the urinalysis sticks do not detect proteins other than albumin. It occurs when there is failure of resorption of proteins secreted by the proximal tubule, and is indicative of proximal renal tubular damage expressed as partial or more generalised Fanconi syndrome (acidosis, hypokalaemia, reduced tubular reabsorption of phosphate and uric acid, normoglycaemic glycosuria or aminoaciduria).

Overflow proteinuria is due to immunoglobulin light chains in multiple myeloma, lysozyme, myoglobin, or haemoglobin.[6] A combination of these different patterns of proteinuria can occur. It is important to understand how to differentiate amongst "benign" transient proteinuria (e.g. only one positive test proteinuria), common causes of pathologic proteinuria (such as diabetic nephropathy, previous known glomerular disease), and molecular targeted therapy (MTT)-induced proteinuria that requires further evaluation and possible kidney biopsy (Fig. 1). In most cases of new or heavy proteinuria (>3 g/day) associated with microscopic haematuria, a kidney biopsy is generally required.

3. Evidence for MTT-induced proteinuria

Anti-VEGF agents are generally well tolerated. Hypertension and asymptomatic proteinuria are common dose-related side-effects that frequently occur together.[7,8] Incidence and rate of proteinuria are variable in different studies according to patients' characteristics, signals targeted and cancer type. Clinical reports suggest that many patients may have increased protein excretion during treatment with bevacizumab. Tables 1 and 2 summarise the National Cancer Institute's proteinuria gradings and findings of the available phase 2 and 3 studies concerning the proteinuria induced by VEGF-targeted therapies.[9–28] Bevacizumab therapy has been associated with the development of proteinuria in 23–38% of patients with colorectal cancer, and in up to 64% of patients with renal cell carcinoma in whom 6.5% experienced a grade 3–4 proteinuria denoting structural damage to the glomerular filtration barrier.[12,29] In the AVOREN (*Avastin* for Renal Cell Cancer) study,[13] out of the 95 patients who received bevacizumab plus interferon alfa for longer than 1 year, 6 and 3% reported grade 3/4 proteinuria and hypertension, respectively. However, in the First Bevacizumab Expanded Access Trial (BEAT) trial, grade 3–5 proteinuria related to bevacizumab was found in only 0.4% of 1903 patients. Furthermore, in the TREE (Three Regimens of Eloxatin Evaluation) trials the incidence of grade 3/4 proteinuria was low and similar in all groups (1%) including the bevacizumab group.[30] A meta-analysis of randomised controlled trials with patients receiving bevacizumab indicated a relative risk of 1.4 for proteinuria with bevacizumab at a low dose (2.5 to 7.5 g/kg) and 1.6 for a high dose (10 to 15 mg/kg)[7] suggesting a dose-dependency to bevacizumab-associated proteinuria. In a phase 1 trial of the small-molecule VEGF receptor antagonist KRN951, 14 of 15 patients developed hypertension and three patients developed dose-limiting proteinuria.[31] Patel et al. reported a preeclampsia-like syndrome characterised by