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Influence of vascular endothelial growth factor inhibition on simple renal cysts in patients receiving bevacizumab-based chemotherapy

Tal Grenader, Linda Shavit[1]

Department of Oncology and [1]*Division of Adult Nephrology, Shaare Zedek Medical Center, Jerusalem, Israel*

Purpose: Although angiogenesis has been implicated in the promotion of renal cyst growth in autosomal dominant polycystic kidney disease, no studies have investigated the role of angiogenesis in the growth of simple renal cysts. The aim of current study was to investigate the effect of chemotherapy with the antivascular endothelial growth factor antibody bevacizumab on renal cyst development and growth in cancer patients.

Materials and Methods: We retrospectively reviewed the medical records of 136 patients with a variety of cancers that were treated with bevacizumab-based chemotherapy for metastatic disease. The presence of and changes in renal cysts were evaluated by retrospective analysis of computed tomography scans performed for assessment of tumor response to bevacizumab-based therapy.

Results: The median age of the patients was 64 years. Renal cysts were identified in 66 patients, in whom 33 (50%) had a single cyst and the rest had 2 or more cysts. The average dose of bevacizumab was 2.68 mg/kg per week. Median duration of treatment was 33 weeks. Average cyst size was 1.9±2.4 cm at the beginning of the study and the majority of the cysts (54 patients, 84%) did not change in size or shape during bevacizumab treatment. No patients were identified with new cysts. Cyst size changed in 10 patients (16%): an increase of 15% to 40% from the baseline size in 5 patients and a decrease in size of 10% to 70% in another 5 patients. The duration of bevacizumab therapy was significantly longer in the subgroup of patients with diminished or increased cyst size than in the patients with stable cyst size: 62 weeks versus 29 weeks, respectively (p=0.0002).

Conclusions: Our data demonstrated that simple renal cysts were stable in size and number in the vast majority of cancer patients treated with bevacizumab.

Keywords: Angiogenesis inhibitors; Bevacizumab; Cysts; Vascular endothelial growth factor receptors

INTRODUCTION

Angiogenesis is defined as the formation of new blood vessels and contributes to embryonic development as well as adaptive revascularization in adults [1]. Recently, angiogenesis was proposed in both animal and human studies as a possible mechanism in the growth of renal cysts [2-6]. Moreover, in animal models, inhibition of the

Received: 14 July, 2015 • **Accepted:** 10 November, 2015
Corresponding Author: Tal Grenader
Department of Oncology, Shaare Zedek Medical Center, P.O. Box 3235, Jerusalem 91031, Israel
TEL: +972-2-6555086, FAX: +972-2-6666731, E-mail: talgrenader65@hotmail.com

mRNA expression of the vascular endothelial growth factor (VEGF) receptors VEGFR1 and VEGFR2 led to significantly decreased tubule cell proliferation, decreased cystogenesis, and blunted renal enlargement and prevented the loss of renal function [6]. On the basis of these emerging findings, we propose that therapeutic strategies that can inhibit angiogenesis may slow the growth of simple renal cysts.

Bevacizumab (Avastin), a recombinant humanized monoclonal antibody against VEGF, was the first angiogenesis inhibitor to be approved for the treatment of cancer. When added to intravenous 5-fluorouracil-based chemotherapy for the first-line treatment of metastatic colorectal cancer, it has been shown to significantly prolong survival [7,8]. Encouraging results have also emerged from clinical trials in non–small-cell lung cancer, breast and renal cell carcinoma, and glioblastoma [9-12]. The potential role of bevacizumab in the prevention of renal cyst growth has not been previously explored.

We hypothesized that bevacizumab administered to control malignancy in patients with cancer may also reduce the rate of cyst growth in patients with simple renal cysts. The aim of this study was to investigate the effect of bevacizumab chemotherapy on renal cyst development and growth in cancer patients.

MATERIALS AND METHODS

Adult patients who received bevacizumab for any cancer at Shaare Zedek Medical Center from January 2005 to November 2011 were selected. The data were retrieved from computerized medical records. Patients were eligible if they were more than 18 years old and received at least 8 weeks of bevacizumab therapy for their malignancy. The minimum dose of bevacizumab was 2.5 mg/kg/week. All patients had at least two consecutive computed tomography (CT) scans. A retrospective analysis of the medical records and sequential CT scans of the eligible patients were then performed. The presence of renal cysts was evaluated by retrospective analysis of CT scans performed as follow-up to assess the response of disease to bevacizumab-based chemotherapy. All CT scans were performed by the same department and with the same device; moreover, the same expert physician evaluated the changes in cyst size and shape. The Bosniak grading classification was used to evaluate the cysts [13,14]. Sequential changes in the size of the renal cysts were evaluated. The rate of increase in cyst size was calculated for each individual.

The Shaare Zedek Medical Center Ethics Committee approved the test protocols. Written consent was not obtained for this study from the individual patients, who remained anonymous, because the study was based on data collected as part of routine clinical care. Statistical analysis was performed with JMP software version 5.0 (SAS Institute Inc., Cary, NC, USA). The association of changes in cyst size with treatment duration, bevacizumab dosage, and the demographic characteristics of the patients was assessed by univariate analysis; nominal and categorical variables were compared by using the Pearson chi-square test. Continuous variables were compared by using the nonparametric Wilcoxon test.

RESULTS

The data from 136 patients (64 males and 72 females) were analyzed. The demographic and clinical characteristics of the study patients are shown in Table 1. The patients' median age was 64 years (range, 35–89 years).

Of the 136 studied patients, renal cysts were identified in 66, in whom 33 (50%) had a single cyst and the rest had 2 or more cysts. The vast majority of the patients (65 of 66) had a category I cyst according to the Bosniak criteria and one patient had a hyperdense benign cyst classified as category II by the Bosniak criteria. The median follow-up was 42 weeks (range, 15–120 weeks). Two patients were lost to follow-up, leaving 64 patients for evaluation. The median duration of treatment was 33 weeks (range, 9–104 weeks). The average dose of bevacizumab was 2.68 mg/kg per week. Average cyst size was 1.9±2.4 cm at the beginning

Table 1. Demographic and clinical characteristics of the study patients

Variable	Patients with cysts (n=66)[a]
Age (y), median (range)	67.5 (38–89)
Sex	
Male	38
Female	28
Primary tumors	
Colon cancer	57
Breast cancer	3
Lung cancer	5
Ovarian cancer	1
Average does of bevacizumab (mg/kg/wk)	2.63
5 mg/kg every 2 weeks (n)	42
7.5 mg/kg every 2 weeks (n)	20
10 mg/kg every 3 weeks (n)	1
15 mg/kg every 3 weeks (n)	3
Median duration of bevacizumab therapy (wk)	31 (8–104)

[a]:Two patients were lost to follow-up, leaving 64 patients for evaluation.

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of the study and the majority of the cysts (54 patients, 84%) did not change in size or shape during the follow-up period. No patients were identified with new cysts. Cyst size changed in 10 patients (16%): enlargement of 15% to 40% from baseline size in 5 patients and a decrease in size of 10% to 70% in another 5 patients. The demographic and clinical characteristics of the patients, broken down by change in cyst size over the follow-up period, are shown in Table 2. Two groups of patients were created: group A (n=54) were patients in whom cysts were stable in size and number; group B (n=10) represented patients with increased (n=5) and decreased (n=5) cyst size. There were no significant differences between the groups in the demographic parameters, primary disease, or dose of bevacizumab. Duration of bevacizumab therapy was significantly longer in the subgroup of patients with diminished or increased cysts size than in the patients with stable cyst size: 62 weeks versus 29 weeks, respectively (p=0.0002).

DISCUSSION

Our study demonstrated that simple renal cysts were stable in size and number in patients with various malignancies treated by bevacizumab. The majority of the cysts (84%) did not change in size or shape during the follow-up period, and no patients with new cysts were identified. To the best of our knowledge, this is the first study that assessed the potential effect of an angiogenesis inhibitor on simple renal cyst growth. These observations suggest that bevacizumab has minimal, if any, inhibitory effects on the rate of cyst growth or on the development of new cysts. Ten patients whose cysts changed in size received bevacizumab-based therapy for a significantly longer time, but cyst size decreased in only five cases. These changes in size were probably the result of longer follow-up, but the impact of bevacizumab treatment cannot be excluded.

Literature review reveals that the natural history of simple renal cysts represents cyst growth in size and number in the majority of cases. Simple renal cysts are commonly observed in normal kidneys and occur mostly in patients over the age of 50 years [15]. The prevalence and sequential changes in size and number of simple renal cysts have been evaluated in several previous studies [16,17]. The prevalence of at least 1 renal cyst on ultrasound has been reported as 11.9% and to increase more than 7 folds with age: from 5.1% in the fourth decade to 36.1% in the eighth decade of life [16]. Our patients were in the sixth to seventh decade and the prevalence of cysts detected by CT scan was about 50%. Literature review revealed that the average increase in size and the rate of enlargement depends largely on the patient's age and ranges between 1.84 and 3.94 mm. and between 3.9% and 6.3% yearly, respectively [15-17]. Renal cysts sometimes increase rapidly in size, especially in younger patients, but stabilize at an older age. Terada et al investigated the 10-year natural history of simple renal cysts and showed that most of them increased in size and number. The average increase in size and the rate of enlargement depended largely on the patient's age (it was more rapid in younger patients) and multiloculated structure [17]. The study by Dalton et al. [18] included 59 patients with simple renal cysts who were followed for up to 39 months. In that study, renal cysts progressed in number rather than in size,

Table 2. Demographic and clinical characteristics of the study patients stratified by changes in cyst size during the follow-up period

Variable	Group A (stable cyst size)	Group B (changed cyst size)	p-value
Age (y), median (range)	68.5 (38–89)	66 (52–75)	0.85
Sex			0.76
Male	31	5	
Female	23	5	
Primary tumors			0.65
Colon cancer	47	8	
Breast cancer	2	1	
Lung cancer	4	1	
Ovarian cancer	1	-	
Average does of bevacizumab (mg/kg/wk)	2.61	2.75	0.96
5 mg/kg every 2 weeks (n)	33	8	
7.5 mg/kg every 2 weeks (n)	18	-	
10 mg/kg every 3 weeks (n)	1	-	
15 mg/kg every 3 weeks (n)	2	1	
Duration of bevacizumab therapy (wk), median (range)	29 (8–104)	62 (30–93)	<0.0002

and exhibited different degrees of aggressiveness. Yasuda et al. [19] monitored 50 patients with renal cysts and found that the size and number of cysts increased with age. In patients with asymptomatic microscopic hematuria, the annual growth rate of simple renal cysts was 4.2% during a 3-year follow-up period in 55 patients and 5.1% during a 6-year follow-up period in 31 patients [20]. Overall, existing data demonstrate that the diameter of a simple renal cyst may increase by approximately 5% annually. Although the clinical significance of simple renal cysts is not completely clear and most patients are asymptomatic, an association of renal cysts with hypertension, higher albumin excretion, and hyperfiltration has been reported. Simple renal cysts are rarely associated with rupture, hematuria, pain, abdominal mass, and infection. In addition, limited evidence suggests that younger patients with simple renal cysts may have mildly reduced renal function [16,21-26]. Increased vascularization is a pattern of malignant lesions. Malignant transformation of simple renal cysts during follow-up, although reported in the literature, is a very unusual clinical scenario. Only a few case reports have been described so far, and a significant increase in the size of renal cysts is not always associated with malignant transformation [21,27,28].

Bevacizumab is a humanized monoclonal antibody against VEGF and is an angiogenesis inhibitor. Recently, angiogenesis was proposed in both animal and human studies as a possible powerful mechanism in the growth of renal cysts. An extensive capillary network in the cyst wall, morphological evidence of vascular malformations, and increased expression of VEGF165 in cyst cells and of VEGFR2 in endothelial cells were all extensively demonstrated in patients with autosomal dominant polycystic kidney disease [2-4]. A possible role for angiogenesis in the early progression of disease in autosomal dominant polycystic kidney disease was confirmed by a clinical study that showed a strong correlation between angiogenic growth factors with both renal and cardiac disease severity [3]. In patients with Von Hippel Lindau disease, a rare genetic disease that is characterized by renal cysts and tumor formation, a 10- and 16-fold increase of VEGF concentration was seen in fluid from two independent Von Hippel Lindau disease-related cysts compared with VEGF serum levels of the same patient [5].

Our study had some limitations. First, it was an observational and uncontrolled study; therefore, we cannot rule out known or unknown confounding factors as an explanation for our results. Second, bevacizumab was administered during a relatively short period of time, leading to possible underestimation of its effect on the growth of renal cysts. Importantly, owing to the observational design of our study, the possibility of residual confounders remains a serious limitation and the only conclusion that can be drawn is an association between bevacizumab administration and stability in size and number of simple renal cysts in cancer patients. Even though our study cannot demonstrate direct causality or help to guide clinicians with treatment decisions, it can be considered as hypothesis generating and serve as a basis for future controlled trials exploring the potential benefits of VEGF inhibition in slowing the growth of renal cysts. We propose that the best way to check whether VEGF inhibition slows the development or growth of simple renal cysts is retroactive measurement of kidney cysts on CT scans obtained for response assessment in randomized placebo-controlled trials of anti-VEGF agents in solid tumors.

CONCLUSIONS

Our data suggest that simple renal cysts are stable in size and number in the vast majority of cancer patients treated with bevacizumab. Further studies will be required to evaluate the influence of other anti-VEGF agents like ramucirumab, aflibercept, sunitinib, sorafenib, and pazopanib on the growth of simple renal cysts.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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