JBUON 2015; 20(3): 923-927
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Feasibility of rapid infusion of the initial dose of bevacizumab in patients with cancer

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Summary

Purpose: *Bevacizumab is a monoclonal antibody against vascular endothelial growth factor (VEGF) widely used in clinical oncology. Bevacizumab is commonly co-administered with chemotherapy. It is recommended that the first infusion of the antibody last 90 min, the second 60 and all subsequent 30 min. Since there is no clear rationale for the proposed schedule of administration, our study assessed the feasibility of a 30 min initial infusion.*

Methods: *Cancer patients eligible for de novo bevacizumab treatment were enrolled. All patients received standard bevacizumab dose of 5, 7.5 or 10 mg/kg according to the indication, diluted in 250 ml normal saline, as a 30-min intravenous infusion.*

Results: *Thirty two patients were enrolled: male 18, female 14, median age 58 years, range 42-78. Oncologic diagnosis: lung cancer 16, colorectal 4, breast 3, ovarian 7, renal 2. All patients tolerated the infusion well. No hypersensitivity reactions were noted. Mean systolic and diastolic blood pressures were 122 and 73 mm/Hg respectively prior to the infusion and 125 and 75 mm/Hg 15 min after the infusion (p=0.3). During the observation period of 1 hour, blood pressure did not change. Transient grade 3 systolic hypertension was noted in 1 patient, with spontaneous regression in 45 min.*

Conclusion: *Rapid administration of bevacizumab in 30 min, rather than the recommended in the package insert 90 min is feasible and safe. Such a practice limits the time of confinement in the treatment area to patients' satisfaction and would result in cost savings by reducing health resource utilization.*

Key words: *bevacizumab, cancer, oncology, short infusion, time savings*

Introduction

Bevacizumab is an antiangiogenic agent with broad application in clinical oncology. It is a recombinant humanized IgG1 monoclonal antibody against VEGF. Bevacizumab has been developed as an antiangiogenic agent for the treatment of solid tumors. While angiogenesis plays a role in physiologic processes such as embryogenesis, wound healing, and corpus luteum formation, angiogenesis has also been implicated in the pathogenesis of a variety of disorders, including the growth and metastasis of solid tumors, intraocular neovascularization, rheumatoid arthritis, and psoriasis [1-6]. VEGF is a secreted, endothelial-specific mitogen. VEGF is encoded by a single gene, but alternative splicing of VEGF mRNA produces 4 different secreted isoforms (121, 165, 189, and 206 amino acids) [7-9]. VEGF exists as a homodimer of 2 identical disulfide-linked subunits and it exerts its effects on the vasculature through high-affinity tyrosine-kinase receptors (VEGFR), whose constitutive expression is restricted to endothelial cells [9]. The growth of solid tumors is dependent on angiogenesis for the supply of nutrients and for the removal of metabolic waste products. Accordingly, elevated levels of VEGF are produced by a variety of tumors resulting in

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Received: 23/12/2014; Accepted: 12/01/2015

the development of tumor feeding vessels. Elimination of VEGF by bevacizumab has resulted in increased responses and survival in multiple tumors [10].

In phase I trials, bevacizumab was first administered by intravenous infusion over 90 min [11]. If the initial infusion was well tolerated, the second infusion was administered in 60 min and all subsequent in 30 min. However, bevacizumab was generally well tolerated and was not associated with acute adverse events. The toxicity of the agent has been well characterized, given its broad application in oncology. Common adverse effects include hypertension, epistaxis, proteinuria, wound healing impairment and less commonly arterial thrombosis or bowel perforation. As these are associated with the pharmacologic action of the agent, namely the cellular transcriptional changes related to the clearance of VEGF from the circulation, it is unlikely that toxicity is related to the speed of administration. Acute hypersensitivity reactions are also extremely uncommon due to the fact that bevacizumab is a humanized antibody [12]. Humanized murine monoclonal antibodies do not elicit a significant immune response [13].

Based on the above rationale, we evaluated the feasibility of infusion of the first dose of bevacizumab in 30 min instead of the recommended 90 min. Such practice, if safe, would result in time and cost savings due to reduced resource utilization and would be preferable to patients.

Methods

Cancer patients who were scheduled to receive bevacizumab-containing treatment at Interbalkan European Medical Center were enrolled in this prospective study, after receiving relevant information and signing a consent form approved by the Institutional Review Board. Patients were required to be >18 years old and to have been diagnosed with a malignancy requiring bevacizumab as part of the standard of care. Exclusion criteria to the use of bevacizumab were applied, namely uncontrolled hypertension, concurrent radiation, brain metastasis, mediastinal tumors invading major vessels, history of bleeding or thrombosis.

All patients received bevacizumab at the recommended dose of 5, 7.5 or 10 mg/kg according to their disease and schedule. Bevacizumab first dose was administered in 30 min, as a steady rate intravenous infusion, diluted in 250 ml of normal saline. The infusion of bevacizumab preceded chemotherapy administration when combined with it. No premedication was required before the administration of bevacizumab.

The primary endpoint of the study was to exclude an increase in either the systolic blood pressure (SBP) or the diastolic blood pressure (DBP) by 10 mmHg at 15 min after the conclusion of the bevacizumab infusion. Secondary endpoints included the elevation of SBP or DBP 60 min following the end of the infusion and the recording of any acute adverse event, such as infusion-related toxicity. The first measurement of blood pressure (BP) was performed just prior to the bevacizumab administration. Following the conclusion of the infusion, BP was measured at 15 and 60 min. Patients were observed for a minimum of 60 min thereafter. All patients were to receive subsequent infusions of bevacizumab in 30 min. Thereafter, clinical monitoring was performed according to routine clinical practice. Proteinuria was not routinely sought unless indicated by clinical parameters.

Statistics

Statistical analyses were performed using paired two-tailed t-test, in order to capture in a more sensitive way possible differences in BP. Separate analysis was performed for SBP and DBP. A sample of 32 patients would suffice to demonstrate a >10 mm Hg difference at the 0.05 level of significance with a power of 80%. For statistical analyses the SPSS statistical package (SPSS Inc., Chicago, Ill) was used.

Results

Thirty two patients were enrolled with 18 males and 14 females. Median age was 58 years (range 42–78). All patients had good performance status (<ECOG 2). Diagnosis is shown in Table 1. Of note, 3 patients received bevacizumab monotherapy.

No adverse reaction occurred during the administration and the subsequent observation period. No patient in the trial discontinued bevacizumab because of hypersensitivity reaction, hypertensive episode or any bevacizumab-related toxicity. The mean SBP prior to bevacizumab was 122.8±9.3 mm Hg and 15 min after the infusion it was 125.7±11.5 mm Hg (p=0.3). DBP was 73.7±5.8 mm Hg before the infusion and 74.8±7.1 after the infusion (p=0.1) respectively (Table 2). There was no further increase at 60 min.

SBP (Figure 1) and DBP (Figure 2) show data individually for each patient. In one female patient with breast cancer, arterial blood pressure increased from 135/80 to 170/90 at 15 min (registered as grade 3 toxicity) and returned to baseline at 60 min. This patient was particularly anxious regarding her chemotherapy which could have affected BP. Apart from this incident, no patient had an increase of SBP by more than 20 mmHg and of DBP by more than 10 mmHg.

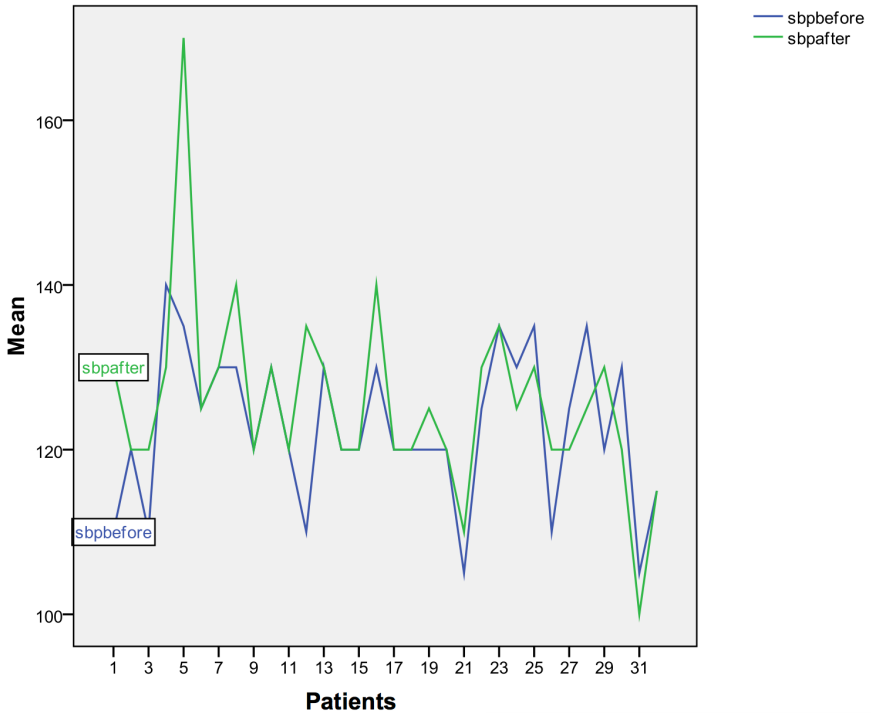

Figure 1. Systolic blood pressure (SBP) before and after the administration of bevacizumab in 30 min (p=0.3).

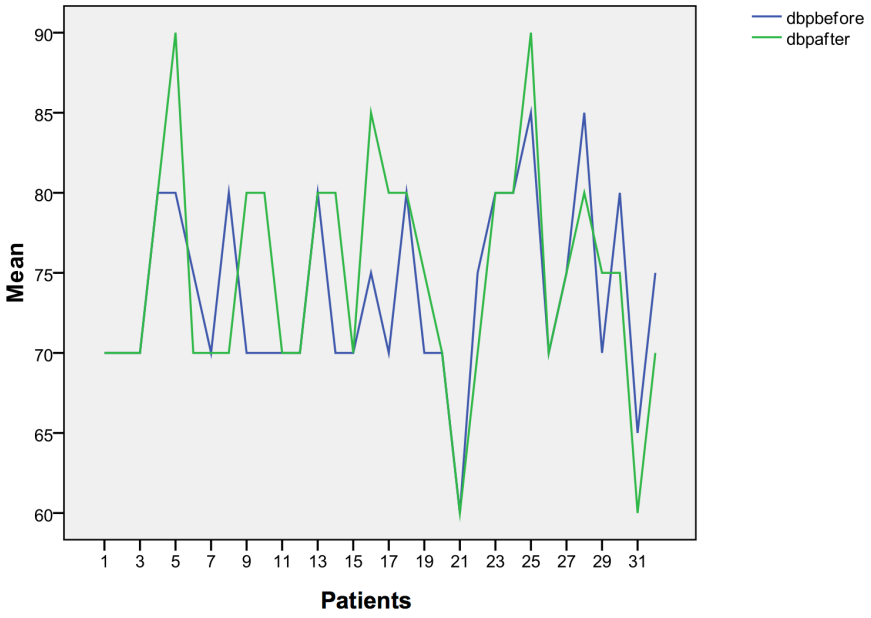

Figure 2. Diastolic blood pressure (DBP) before and after the administration of bevacizumab in 30 min (p=0.1).

Discussion

This study was designed to evaluate the safety and feasibility of a 30-min first bevacizumab infusion rather than the recommended 90-min. Our results indicate that administration of bevacizumab in 30 min from the onset of treatment is safe and can be considered as a way of expediting cancer treatment delivery. This is particularly important as bevacizumab is frequently co-administered with chemotherapy drugs, rendering the whole treatment lengthy. Obviously, reduction of treatment time is desirable by cancer patients. The proposed shortening of bevacizumab administration reduces resource utilization. In many Health Systems the applied charges of chemotherapy administration depend on the duration of infusion. For example, in USA Medicare charges $24 more if the infusion increases from 30 min to 90 min (2008, California, Medicate fee schedule). Faster patient throuput leads to lower patient burden in the clinic, less chair time and less personnel. Therefore, using short infusions and subcutaneous route of drug administration contribute to lowering treatment costs [14] which has become a major issue in modern medicine, as it results in cost savings.

In theory, it is unlikely that the speed of the infusion would affect long-term toxicity, which is rather due to the pharmacologic result of VEGF elimination. Bevacizumab mode of action is indirect; the elimination of VEGF, even if it occurs immediately upon the infusion of bevacizumab, mediates its action to endothelial cells by its absence, by the withdrawal of its positive signal. Conceptually, the speed of the clearence of VEGF should not have any impact on its untoward activity, as the effort requires a gradual turning off of secondary transcriptional processes. Therefore, the biologic result of the "starvation" of VEGF requires some time to take place. Changes of infusion duration are not expected to have a significant impact on these biologic changes.

Table 1. Demographics of 32 patients

Demographics	*N*	*%*
Gender		
Male	18	56
Female	14	44
Type of cancer		
Lung	16	50
Colorectal	4	12.5
Breast	3	9.4
Ovarian	7	21.8
Renal	2	6.3
ECOG performance status		
ECOG 1	24	75
ECOG 0	8	25
SBP		
SBP baseline		
Mean	122.8	
Range	105-140	
DBP baseline		
Mean	73.7	
Range	60-80	

The established guidelines for bevacizumab administration according to package insert, i.e. first infusion in 90 min, second infusion in 60 and subsequently in 30 is rather a result of a cautious empirical approach than a scientifically based schedule. Rapid infusion of a humanized antibody, such as bevacizumab, is not likely to produce any immediate allergic reactions. The only possible concern could be the development of hypertension, plausibly via a fast action on endothelial status and nitric oxide production. However, our data indicate that immediate hypertension is not a clinical problem. Accordingly, equivalence of long term toxicity has been demonstrated in a prospective fashion [15]. This is consistent with

Table 2. Systolic and diastolic blood pressure 15 min before and 15 min after bevacizumab administration. Differences were nonsignificant (p>0.05)

	SBP before	*SBP after*	*DBP before*	*DBP after*
N	32	32	32	32
Mean	122.81	125.78	73.75	74.84
Median	120.00	125.00	70.00	75.00
SD	9.327	11.508	5.820	7.126
Minimum	105	100	60	60
Maximum	140	170	85	90

SBP: systolic blood pressure, DBP: diastolic blood pressure

findings by others who tested rapid infusion only at the dose of 5 mg/kg [16].

In conclusion, our data support the notion that the first dose of bevacizumab can be rapidly and safely infused in 30 min. In particular, rapid infusion does not result in a SBP or DBP elevation. Rapid infusion results in reduced time spent in the oncology treatment area, clearly a desirable goal for health systems but even more importantly for patients.

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