Blood pressure monitoring in patients receiving bevacizumab

We have read with great interest the prospective study by Shah et al. [1] assessing the safety of short infusions of bevacizumab. The authors report similar rates of proteinuria and hypertension in patients receiving the standard infusion regimen (over 90, 60 then 30 min), compared with shorter administrations with an infusion rate of 0.5 mg/kg/min.

Although we agree with Shah et al. that shorter infusions appear safe in terms of short-term reactions as well as cumulative vascular toxic effects [2, 3], we would like to point out potential weaknesses of this prospective study.

First, the rhythm of assessment of blood pressure is not detailed. We have previously shown that assessing blood pressure only before each infusion detects significantly less cases of hypertension than daily blood pressure monitoring did [4].

Second, the authors do not mention the use of a validated blood pressure measurement device, as recommended in recent international recommendations [5].

Third, hypertension grading used in this study was based on NCI-CTC v3.0, with a modified definition for grade 4 hypertension. As well, we have previously shown that NCI-CTC v3.0 allowed the detection of bevacizumab-induced hypertension in significantly fewer cases than the ESH (European Society of Hypertension) classification did [5]. Notably, the recent NCI-CTC v4.0, which was not available at the time of the study by Shah et al., is quite similar to the ESH classification.

As a consequence, we should keep in mind that the proportion of patients developing hypertension in both the prospective and retrospective arms of this study may be under-estimated.

The use of intensive blood pressure monitoring and the recent NCI-CTC v4.0 classification for hypertension grading should be generalized in further studies of hypertension induced by anti-vascular endothelial growth factor (VEGF) agents, as stressed by recent recommendations. Moreover, these tools should also be implemented in routine clinical practice, in particular in real-life populations of patients, as seen in the study by Shah et al. (with up to 50% of patients receiving anti-hypertensive drugs before initiation of bevacizumab).

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disclosure

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Response to letter titled: blood pressure monitoring in patients receiving bevacizumab

Our prospective, observational study was designed to evaluate shorter bevacizumab infusions and the risks of proteinuria and hypertension. As mentioned in the study, blood pressure was assessed before every bevacizumab therapy. A study by Mir et al. suggested that home-based twice-daily blood pressure monitoring may provide a more accurate assessment of the incidence of hypertension compared with blood pressure measured in the clinic [1]. In that study, daily blood pressure monitoring was able to detect a higher incidence of grade 1 hypertension. However, the incidence of ≥ grade 2 hypertension was similar between daily-home- and clinic-based monitoring. Daily blood pressure monitoring warrants further investigation. To our knowledge, none of the current published hypertension guidelines recommend daily blood pressure monitoring. Self-home monitoring is recommended by JNC 7 and European Society of Hypertension (ESH), but these guidelines do not recommend the frequency of self-home
monitoring. Self-home monitoring is recommended by these guidelines to assess anti-hypertensive medication response, to improve patient compliance with therapy and to evaluate white-coat hypertension [2–4]. However, self-home monitoring may also cause anxiety and lead to self-modification of treatment by patients.

In our study, blood pressure was measured before every cycle of bevacizumab and utilized institution-approved automated blood pressure measurement devices in the oncology clinic to maintain consistency with the comparator retrospective arm. Most of the phase III clinical trials listed in Table 4 of our study did not report the frequency of assessment of blood pressure, except a study by Tol et al. which was detailed once every 3 weeks [5]. In addition, our study was an observational study designed to evaluate the safety of shorter infusions and the focus was not to change the current practice standards of blood pressure monitoring.

We do agree with Coriat et al. that if ESH or NCI-CTC v4.0 hypertension classification was utilized, the incidence of hypertension would have been higher in our study. This is especially due to lower threshold for assessment of grade 1 hypertension based on the systolic and diastolic blood pressure values. However, we do not agree that it is a limitation of the study since the same instrument, NCI-CTC v3.0, was utilized to assess the incidence of hypertension in both prospective and retrospective arms of the study.

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Comment on: management of chemotherapy extravasation: ESMO–EONS clinical practice guidelines

Recently, the ESMO–EONS clinical practice guidelines on the management of chemotherapy extravasation was published [1]. Several considerations must be discussed about this issue.

The literature addressing extravasation management is limited to animal studies, case reports and small human studies. Classic randomised studies in humans for the treatment of extravasations are unthinkable because of ethical reasons. Studies in animals are generally carried out in murine models. Because of the potential problems of drug testing in rat skin, which has a thin layer of subdermal muscle (panniculus carnosus), the best model of human skin for intradermal drug testing is the use of white swine [2]. However, studies on such model are scarce. On the whole, the highest possible grade of recommendation of each measure for extravasations would be low.

Extravasations, especially those caused by vesicant agents such as anthracyclines, can be devastating if untreated, resulting in a very high risk of the formation of ulcers and tissue necrosis, even loss of limb function [3]. A control group with placebo is unconceivable and, as defined by Pérez-Fidalgo et al., ‘a comparative study with a control group receiving the standard local care would allow clinicians to clearly define the efficacy of an antidote’ [1].

The majority of human data on anthracycline extravasations treatment include the use of dimethyl sulfoxide (DMSO) 99% combined with cooling or dexrazoxane [4]. These agents were included as treatment options in extravasations occurred during anthracycline treatment with the same grade of recommendation (IIIB) [1]. Surprisingly, Table 5 lowered the level of recommendation of topical DMSO treatment to IV-B, without referencing in the main text or further explanation. We understand that both agents must have the same grade of recommendation due to similar efficacy rates and experience described in the literature [1, 4]. A strong debate is open to determine which specific situations are suitable to use one agent or the other. The most obvious situation may be the use of dexrazoxane as a systemic antidote if an anthracycline extravasation from a central venous access occurred. Dexrazoxane is the only licensed drug for the treatment of anthracycline extravasation. However, a number of questions arise regarding the use of this antidote; the most important one is the lack of a comparative study against DMSO 99% (control arm, standard local care). Moreover, a major concern is the systemic adverse events of dexrazoxane and the financial burden to maintaining dexrazoxane in a hospital’s inventory, which is of utmost importance nowadays.