Key Points

1. Determine the patient's or referring doctor's agenda.
2. Adapt your approach to the consultation agenda.
3. Build confidence in previous care wherever appropriate.
4. Avoid minor variations that do not influence outcome.
5. Be aware of temptations to boost your ego.
6. Pay extra attention to communication.
7. Try to find some added value, by paying attention to issues that are often overlooked.

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Hoarseness during treatment with bevacizumab and other vascular endothelial growth factor signalling inhibitors

HILDA WONG, THOMAS YAU, CHAN WAI MAN & RICHARD J. EPSTEIN

Division of Haematology/Oncology, Department of Medicine, The University of Hong Kong, Hong Kong

To the Editor

The advent of drugs targeting the ubiquitous vascular endothelial growth factor (VEGF) signalling pathway has been a breakthrough in anticancer therapeutics. Several drug classes contribute to this new clinical group: orally bioavailable small-molecule inhibitors of VEGF receptors, such as sunitinib; antibodies to the VEGF ligand (bevacizumab); antibodies to the extracellular domains of VEGF receptors; or decoy fusion receptors, such as aflibercept. Though collectively classified as anti-angiogenic drugs, these VEGF antagonists have also been noted to act as chemosensitizers, most likely by lowering the Akt-dependent apoptotic threshold of tumor cells expressing VEGF receptors [1]. Common side-effects of VEGF signalling inhibition include hypertension, proteinuria, thrombosis, haemorrhage, reduced wound healing, and gut perforation [2]. Voice changes have also been occasionally observed following the use of small-molecule VEGF receptor signalling antagonists such as sorafenib [3], cediranib [4], axitinib [5] and others [6]. Below are described four cases of hoarseness associated with the use of VEGF inhibitors, three of which followed bevacizumab infusions.

Case studies

Case 1. A 43-year-old female with metastatic breast cancer was treated palliatively with bevacizumab and paclitaxel. Restaging with CT scan after four cycles

Correspondence: Richard J. Epstein, 4/F, Professorial Block, Queen Mary Hospital, Pokfulam, Hong Kong. Tel: 852 2855 3994. Fax: 852 2816 2863. E-mail: repstein@hku.hk

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of this regimen confirmed disease shrinkage, but worsening hoarseness at this same time raised concerns of a mixed response, with possible occult disease progression in the mediastinum or brachial plexus. Indirect laryngoscopic evaluation at that time confirmed a unilateral vocal cord palsy, and the patient was recommended to undergo laryngoplasty. Due to a single case report associating paclitaxel with laryngeal disorders [7], however, this drug was initially stopped and capecitabine substituted with continuation of bevacizumab. Vocal dysfunction persisted, but did not worsen, until treatment cessation and death several months later.

Case 2. A 46-year-old man with metastatic renal cell carcinoma was treated with sunitinib, initially using a 50 mg/day four-weeks-on, two-weeks-off schedule. Disease response was evident at first, but was accompanied by refractory progressive vocal hoarseness that rendered the patient virtually aphonic. Sunitinib toxicity became apparent as both cytopaenias and the terminal complication of a bronchopleural fistula. Despite discontinuation of sunitinib and substitution of temsirolimus, vocal dysfunction continued until death five months later.

Case 3. A 41-year-old man with metastatic leiomyosarcoma was treated with gemcitabine and docetaxel with good response. Subsequently, the disease recurred in the right hip and lungs, and the patient was successfully re-treated with radiotherapy and three-weekly cycles of bevacizumab, gemcitabine and (initially) docetaxel. However, after each bevacizumab infusion, the patient reported the onset of marked hoarseness that persisted for about two weeks, and which became worse with successive cycles. Medical treatment was discontinued for three months, during which time the hoarseness resolved.

Case 4. A 39-year-old female patient with relapse of breast cancer in the skin underwent chemotherapy using bevacizumab, gemcitabine and vinorelbine. Following the second cycle, she reported the onset of vocal hoarseness within 48 hours of the bevacizumab infusion, and this recurred during subsequent cycles. However, this toxicity appeared both tolerable and reversible, and regressed following discontinuation of treatment.

The physiologic importance of VEGF signalling in the larynx remains incompletely defined. VEGF may either promote [8], inhibit [9], or have no effect [10] on laryngeal wound healing. Laryngeal inflammation due to either reflux [11] or Reinke's oedema [12] has been positively associated with VEGF upregulation, though this would predict an anti-laryngitis effect of VEGF signalling inhibition. The invasive behavior of laryngeal squamous carcinoma has been linked to VEGF expression intensity [13]. In this report, the implication that both bevacizumab and sunitinib caused similar vocal changes – combined with other reports, cited above, of hoarseness occurring with VEGF receptor kinase inhibitors – is persuasive evidence that this toxicity specifically reflects VEGF signalling inhibition. Neurotoxicity may also be a side-effect of anti-angiogenics [2], and the finding in Case 1 of a unilateral cord palsy in the absence of a mass lesion is certainly consistent with the possibility of a vasculopathic nerve lesion.

The foregoing cases suggest that early recognition of VEGF-dependent vocal pathology is important. If symptoms are severe and/or progressive, immediate discontinuation of the anti-angiogenic drug may be prudent, as the possibility of a persistent deficit seems real. The pathophysiology of this complication remains unclear, though it is possible that it relates to vasculopathic laryngeal nerve damage. Whether drugs such as steroids or antiplatelet agents may be helpful in prevention or treatment is not yet clear, and could be studied in future patients.

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Uncommon long-term survival in a patient with chronic myeloid leukemia

FABIO STAGNO[1*], PAOLO VIGNERI[2*], VITTORIO DEL FABRO[1], STEFANIA STELLA[2], SALVATORE BERRETTA[1], MICHELE MASSIMINO[2], ELENA TIRRÒ[2], ANGELO MESSINA[2] & FRANCESCO DI RAIMONDO[1]

[1]*Department of Biomedical Sciences, Section of Hematology, University of Catania, Italy and* [2]*Department of Biomedical Sciences, Section of General Pathology, University of Catania, Italy*

To the Editor

The introduction of Imatinib Mesylate (IM) has revolutionized the treatment of patients with Chronic Myeloid Leukemia (CML) in chronic phase (CP), resulting in high rates of hematologic, cytogenetic and molecular responses [1]. Clinical evidence estimates 89% of overall survival (OS) at 60 months for patients receiving IM on an intention to treat basis [2]. Before the advent of IM, conventional cytotoxic chemotherapy had failed to cure CML and standard treatment for CP-CML was alpha-interpheron (IFN), which demonstrated an OS at 10 years of 20–53% [3]. On this basis, CML clinical progression to a fatal blast crisis was inevitable [4] and long-term survival in patients with CML extremely unusual. Here we report the case of a patient with CML that represents, to the best of our knowledge, one of the longest survivors described so far in the literature.

A 47-year-old female was referred to a civic hospital in 1986 because of fever and leukocytosis and was diagnosed with CP-CML. She was started with Busulphan (BU) therapy (at conventional doses) as first line treatment, achieving a complete hematological response (CHR) within two months. The patient, in CHR and overall good clinical standing, was maintained in follow-up without further treatment. During this period of time, the white blood cell (WBC) count was normal and the spleen was not enlarged. In December 1997 she lost her CHR, presenting with leukocytosis (WBC 25.000/ mmc). She was then retreated with BU for five months obtaining a second CHR. In January 2004, the patient again displayed high WBC counts (21.000/ mmc) and mild hepato-splenomegaly and

*Authors equally contributed to this work.

Correspondence: Fabio Stagno, Department of Biomedical Sciences, Section of Hematology, Ferrarotto Hospital, via S. Citelli 6, 95124, Catania, Italy. Tel: +39 095 7436100. Fax: +39 095 365174. E-mail: fsematol@tiscali.it

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