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SHORT COMMUNICATIONS AND CASE REPORTS

Implication of bevacizumab in fatal arterial thromboembolic incidents

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Summary

Bevacizumab, a humanized monoclonal antibody against vascular endothelial factor (VEGF), is approved for the treatment of metastatic colon cancer, but it has also shown efficacy in first line therapy of non-squamous-cell non-small-cell lung cancer, breast cancer and clear-cell renal cancer. Antiangiogenic therapy severe toxic effects such as stroke, myocardial infraction, angina, arterial thromboembolism, pulmonary embolism or haemorrhage, gastrointestinal perforation, heart failure should be taken into account during treatment with bevacizumab. We describe and discuss two cases of cancer patients who developed fatal arterial thromboembolic episodes after administration of bevacizumab. Due to the recent launch of antiangiogenic agents and the limited experience with their use in clinical practice, their adverse effects and pharmacological toxicities, sometimes fatal, are not well-established and a detailed registration of them is needed.

Key words: arterial, bevacizumab, cancer, thromboembolic, VEGF

Introduction

Antiangiogenic therapy for specific cancer types has shown modest clinical benefits when used in combination with conventional chemotherapy. Bevacizumab, a humanized monoclonal antibody against VEGF, is the first antiangiogenic drug approved by FDA for the treatment of metastatic colon cancer, but it has also shown efficacy in first line therapy of non-squamous-cell non-small-cell lung cancer, breast cancer and clear-cell renal cancer [1,2].

VEGF family constitutes a key area of basic investigation regarding the way of signal transmission through the VEGF receptor 1 and 2 during angiogenesis. This family of structurally related molecules includes VEGF-A, the main mediator, VEGF-B, VEGF-C, VEGF-D and placental growth factor (PlGF) [3]. VEGF blockage as monotherapy has been shown to have a direct and rapid effect in tumor, presumably through deprivation of tumor vascular supply and inhibition of endothelial proliferation. This blockage appears more efficacious combined with chemotherapy because it results in "normalization" of tumor vasculature permitting the cytotoxic drugs to penetrate easier inside the tumor.

However, due to the recent launch of these agents and the limited experience with their use in clinical practice, their adverse effects and pharmacological toxicities, sometimes fatal, are not well-established and a detailed registration of them is needed.

Case presentations

Case 1

A 52-year-old male suffering from an extensive adenocarcinoma of the right lung (T4) with infiltrated mediastinal lymph nodes (N2) and bone metastases involving the thoracic vertebra 10 (T10) and the right humeral bone (M1) had initially received 2 cycles of chemotherapy with carboplatin/etoposide without response. He was then treated with erlotinib and palliative

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radiotherapy again without response. Finally, it was decided to start treatment with bevacizumab every 2 weeks at dose of 10 mg/kg [4]. Eight days after the first administration of bevacizumab thrombosis of the right tibial artery occurred (Figure 1). Treatment with intensive anticoagulant therapy was ineffective resulting in extensive necrosis of the right leg. Despite salvage surgical and supportive efforts the patient died 20 days after the diagnosis of thrombosis.

Case 2

A 43-year-old female with relapse of a spindle-cell sarcoma of the maxilla inferior was treated with second-line chemotherapy with liposomal doxorubicin/dacarbazine/ifosfamide. Relapse was locoregional and distant with lung and small liver metastatic lesions (stage IV). Respiratory function, although influenced, was satisfactory. After 4 cycles of chemotherapy a stable disease status was achieved. In order to improve the results of chemotherapy it was decided to add also bevacizumab every 2 weeks at a dose of 10 mg/kg [5]. Four days after the second administration of bevacizumab the patient developed a typical symptomatology of pulmonary embolism. Pulmonary hematosis scintigraphy revealed embolization of the anterior basal section of the right lung (Figure 2). Intensive anticoagulant therapy was initiated immediately but, despite a temporary improvement after 7 days of treatment, a gradual deterioration of respiratory function developed evolving to acute respiratory distress syndrome and finally resulting in death 21 days after the diagnosis of pulmonary embolism.

Discussion

Antiangiogenic therapy has toxic effects and often is being administered in patients with other co-morbidities. Bleeding, gastrointestinal perforation, hypertension, nephrotic syndrome, reversible posterior leukoencephalopathy syndrome (RPLS), wound dehiscence should be of concern during treatment with bevacizumab. More severe cardiovascular adverse effects such as stroke, myocardial infraction, angina, arterial thromboembolism, pulmonary embolism or haemorrhage, gastrointestinal perforation, heart failure –especially in combination with anthracyclines– are also triggered due to the drug's mechanism of action, the pre-existence of cardiovascular disease and the cancer-related predisposition to thrombosis [4,6-9].

Since the addition of bevacizumab to conventional chemotherapy seems to be helpful in fist line therapy in specific cancers, it is necessary to understand the pathology of bevacizumab-related thromboembolic events and try to minimize them. A lot of research is being conducted in order to give answers to these clinical concerns: Which subgroup of patients would suffer of thromboembolic events mostly? Could or should they be protected using anticoagulation factors during therapy or the incidence of bleeding will rise? Are there any predisposing factors (e.g. protein C, S deficiency, mutated V Leiden factor etc) which contribute to thrombosis during treatment with bevacizumab? Gastrointestinal cancers themselves can cause thromboembolic events. In which proportion can they promote thromboembolism since bevacizumab's first indication is metastatic colorectal cancer?

Another clinical observation is also of great interest. When bevacizumab is added to conventional chemotherapy the risk of arterial thromboembolism increases but it is comparable to the risk of venous thromboembolism in patients who receive only conventional chemotherapy [3]. Some studies have also implied that chemotherapy dose can contribute to clot formation when combined with antiangiogenic factors [10].

In conclusion, further research is necessary to clarify the mechanism of the enhanced coagulation during treatment with bevacizumab and conventional chemotherapy and give answers to clinical concerns. These answers will secure patients maximizing the clinical benefit of antiangiogenic treatment.

Figure 1. Thrombosis of the right tibial artery after treatment with bevacizumab.

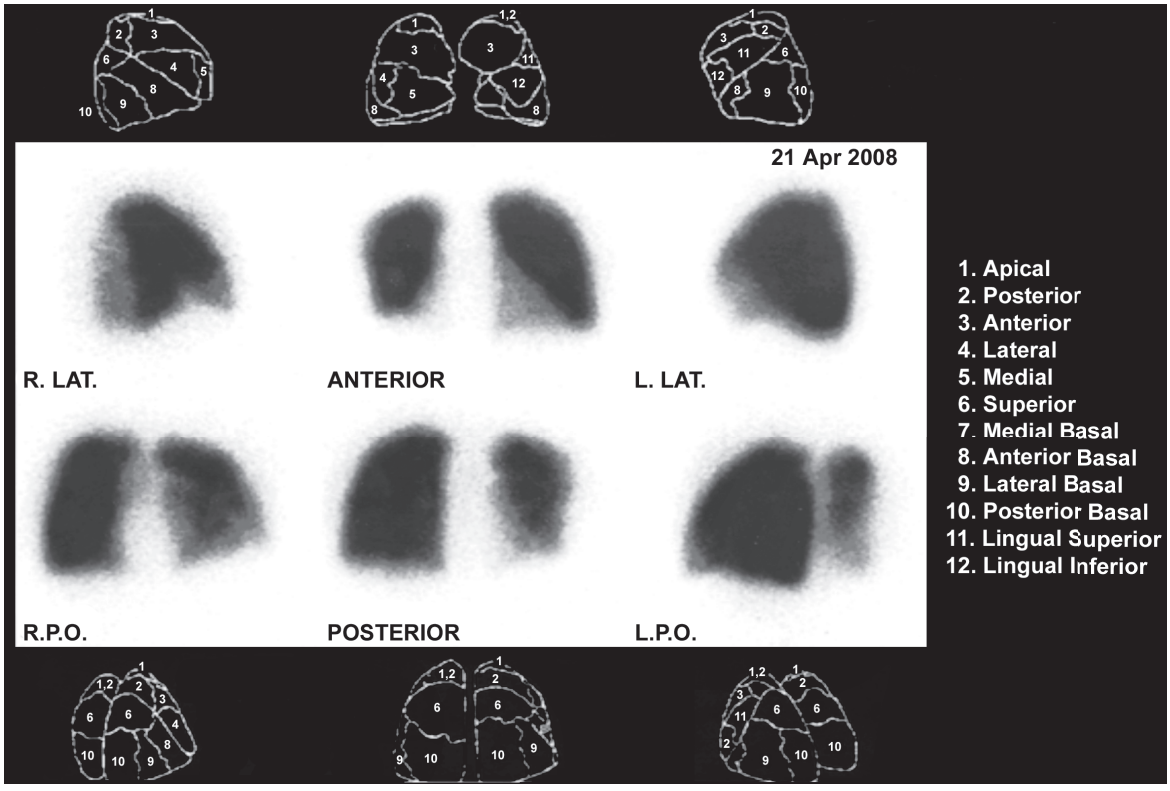

Figure 2. Tc-99m-MAA pulmonary hematosis scintigraphy shows arterial embolism of the anterior basal section of the right lung after bevacizumab administration.

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