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Side effects of anti-angiogenic drugs

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ABSTRACT

Anti-angiogenic drugs and in particular anti-vascular endothelial growth factor (VEGF) agents have entered the clinical armamentarium against cancer. New unexpected toxicities have emerged. The incidence and the severity of these toxicities have a great variability in the different studies. Among them, bleeding is one of the most severe and difficult to manage. Bevacizumab retains the highest frequency of bleeding complications, in particular epistaxis, hemoptysis and gastrointestinal bleeding. Although a higher incidence of severe hemorrhages has not been consistently demonstrated during the treatment with bevacizumab, mild bleeding episodes appear clearly increased in the experimental arm of most trials. Cases of severe pulmonary hemorrhage were reported in patients with lung cancer; these events occurred mainly intra-tumor and were significantly associated with squamous cell histology. Trials with other small-molecule tyrosine kinase inhibitors like sunitinib or sorafenib showed an overall lower rate of bleeding complications, but still significantly higher than the control arm in many cases.

The mechanisms of bleeding induced by anti-VEGF agents are complex and not yet fully clarified: the main hypothesis is that VEGF could promote endothelial cell survival and integrity in the adult vasculature and its inhibition may decrease the renewal capacity of damaged endothelial cells. Management of bleeding in patients treated with anti-VEGF agents is a challenging task because this complication is at least in part inherent to the efficacy of the drug and because there is also an increased risk of thrombosis, both arterial and venous. So far, only few preliminary data are available on a strategy to prevent hemorrhage and thrombotic event.

1. Introduction

With the introduction of novel anti-angiogenic drugs in the treatment of cancer, new unexpected toxicities have been observed requiring new strategies for their management. Since for many of them the pathogenesis of these toxicities is strictly dependent on the mechanism of action of anti-angiogenic drugs, reducing toxicity without limiting the therapeutic effect is a challenging task.

Vascular endothelial growth factor (VEGF) plays the most important role in the regulation of tumor-related angiogenesis and its expression seems very limited in adult tissues, making it a preferred target for anti-tumor therapy. In fact, higher VEGF expression is associated with greater tumor invasiveness and metastatic ability. In addition, VEGF inhibits endothelial cell apoptosis and increases tumor interstitial pressure, reducing the penetration of cytotoxic drugs into the tumor mass [1]. It is clear that the blockade of VEGF pathways is of particular interest in stopping tumor growth and in enhancing the efficacy of other chemotherapeutic combinations. However, the same mechanisms (inhibition of apoptosis, vasodilatation/vascular permeability, reduced vascular density) are the basis for the main toxicities of anti-VEGF agents. Some anti-VEGF agents have received FDA approval for different cancers and are increasingly used in clinical practice, including the humanized monoclonal antibody against VEGF bevacizumab for colorectal cancer and renal cell carcinoma, and the small-molecule multi-target tyrosine kinase inhibitors sunitinib (SU11248) and sorafenib (BAY 43-9006) for renal cell and hepatocellular carcinoma and for gastrointestinal stromal tumors (GIST). Pazopanib is the more recent small-molecule tyrosine kinase inhibitor which has been approved by the FDA for the treatment of renal cell carcinoma. Many other agents are used in clinical trials and they will enter soon the daily armamentarium for the treatment of cancer. The incidence and the severity of the toxicities reported in different studies is very variable, also within the same class of molecules or with the same agent used in different types of tumors. So, notably, the toxicity of anti VEGF agents includes hypertension, proteinuria, bleeding, gastrointestinal perforation, impaired wound healing, and arterial and venous thromboembolism [2].

A good example for this variability is hypertension, one of the most commonly reported toxicities of anti-VEGF agents: hypertension resulted to be the dose-limiting toxicity (DLT) in the first studies with the new molecules axitinib and cediranib, but this

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was not the case of the previously approved molecules [3,4]. In addition, although this complication seems dose-dependent, a direct relationship between total dose of the drug and blood pressure has been observed only for some agents (e.g. sunitinib), but not for others (e.g. axitinib) [5,6]. Treatment-induced hypertension reflects the effect of anti-VEGF agents on multiple receptors to VEGF (VEGFR), which are present on the vasculature throughout the body, and the different affinity of each anti-VEGF agent for the different VEGFRs may explain this variable behavior.

This wide variability, together with the fact that randomized clinical trials are powered to compare the efficacy and not the toxic effects of the drugs, makes it often difficult to establish if a particular toxicity is really increased by the addition of an anti-angiogenic drug to the standard treatment.

This review will be focused on hemorrhagic complications of anti-angiogenic drugs.

2. Incidence of hemorrhagic complications

Bleeding is one of the most severe and potentially life-threatening toxicities of anti-angiogenic drugs, with a wide range of incidence and severity in different studies. Bevacizumb retains the highest frequency of bleeding complications, including epistaxis, hemoptysis, hematemesis, gastrointestinal or vaginal bleeding, and brain hemorrhage.

Although a pooled analysis of three randomized trials failed to demonstrate a significantly higher incidence of severe hemorrhages (grade 3 and 4) [7], the incidence of mild bleeding episodes is clearly increased in the experimental arm of most trials (up to 40%, as shown in Table 1), while the rate of severe complications is significantly higher only in few trials. Life-threatening or fatal episodes were also reported [8,9]. In the full safety population of 1,132 patients with different tumor types, the incidence of grade 3 and 4 bleeding events was 4.0% [10]. Mild mucosal bleeding and in particular epistaxis (grade 1 and 2) are the most common form of hemorrhagic toxicity associated with bevacizumab and usually resolve without medical intervention. The already mentioned hypertension associated with the use of anti-angiogenic drugs may further contribute to the occurrence of epistaxis, but other factors like the anatomical site of the tumor, the cancer histology, the type of associated chemotherapy, or the bevacizumab dose may be important in the manifestation of mild or severe hemorrhages.

In two trials using bevacizumab, paclitaxel and carboplatin for patients with lung cancer, severe bleeding events occurred mainly intra-tumor and pulmonary hemorrhages were associated with squamous cell histology [9,11]. In particular, life-threatening pulmonary hemorrhage and/or hemoptysis were observed in six out of 66 patients (9%) with non-small-cell lung cancer (NSCLC) treated with bevacizumab, with four of these episodes being fatal. Based on a multivariate analysis, patients with squamous cell histology had the highest risk of hemorrhage [9] and therefore patients with this histology have been excluded from subsequent studies. The ECOG 4599 (Easter Cooperative Oncology Group 4599) trial excluded also patients with brain metastases, previous hemoptysis, poor performance status, or with ongoing treatment with anticoagulants or nonsteroidal anti-inflammatory drugs. However, these restrictions strongly limit the rate of patients still eligible for a treatment with bevacizumb: in fact, only 30% of patients with advanced NSCLC were eligible for the ECOG 4599 trial due to these safety restrictions [12]. Furthermore, it is difficult to avoid pulmonary hemorrhages in this setting if they are related to the efficacy of bevacizumab itself, with many lung tumors being necrotic or having central cavitation, or with the proximity of the tumor itself to a major blood vessel. In a retrospective multivariate analysis of clinical or radiological risk factors for pulmonary hemorrhage in two trials, only baseline tumor cavitation, but not tumor location, emerged as a significant risk factor for severe hemorrhage [13].

In general, the trials with the small-molecule tyrosine kinase inhibitors showed a lower rate of bleeding complications, but it was still significantly higher than in the control arm in many cases (see Table 2). Mild epistaxis was more common (12% vs. 1%) in the sunitinib arm than in the interferon alpha arm of a phase III study for renal cell carcinoma [14], fatal pulmonary hemorrhages occurred in two patients in a trial of sunitinib in metastatic NSCLC [15], and therefore the agent has not been approved for this form of cancer. No difference in bleeding events between sunitinib and placebo (18% vs. 17%) was found in patients with GIST [16]. A higher rate of bleeding was observed in the sorafenib arm (15% vs. 8%) of a phase III trial in renal cell carcinoma [17], but severe hemorrhages were comparable (3% vs. 2%). Two other studies in renal cell carcinoma [18] and pancreatic cancer [19] failed to show an increased incidence of grade 3–4 bleeding events. In a meta-analysis of 27 trials with sunitinib and sorafenib, the overall bleeding rate was 16.7%, with 2.4% of severe events [20].

3. Pathogenesis

The mechanisms of anti-VEGF agents-induced hemorrhage are complex and not yet fully clarified. The tendency to bleeding after inhibition of the VEGF-dependent signalling reflects the physiological activities of VEGF on vascular walls and perhaps on the clotting system. The main hypothesis is that inhibition of VEGF decreases the renewal capacity of endothelial cells after a trauma.

Table 1
Incidence of overall and grade 3–4 bleeding events in patients treated with bevacizumab and chemotherapy for different solid cancers.

Therapy	Tumor	All bleeding events	Grade 3–4 bleeding episodes	Reference
Bevacizumab (5 or 10 mg vs. control) + fluorouracil + leucovirin	metastatic colorectal cancer	52% (low-dose) vs 69% (high-dose) vs. 11% (controls)	0% in low-dose vs. 9.4% in high-dose vs. 0 % in controls	Kabbinavar, 2003 [29]
Bevacizumab + oxaliplatin + fluorouracil + leucovirin	advanced or metastatic colorectal cancer	43%	2.3%	Giantonio, 2006 [30]
Bevacizumab (vs. placebo) + oxaliplatin + fluorouracil + leucovirin (FOLFOX4)	metastatic colorectal cancer	not reported	3.4% vs. 0.4% (P = 0.011); 1 fatal event	Giantonio, 2007 [31]
Modified FOLFOX6 alone or + bevacizumab (TREE Safety Study)	metastatic/recurrent colorectal cancer	45% vs. 22%	3% vs. 0% in controls	Hochster, 2008 [32]
Adjuvant bevacizumab (vs. placebo) + oxaliplatin + fluorouracil + leucovirin	stage II–III colon cancer	1.9% vs. 1.9%	not significantly different	Allegra, 2009 [33]
Bevacizumab (vs. placebo) + capecitabine	relapsed metastatic breast cancer	28.8% vs. 11.2%	0.4% vs. 0.5% (NS)	Miller, 2005 [34]
Bevacizumab (vs. placebo) + paclitaxel + carboplatin	advanced or metastatic non-small-cell lung cancer (not squamous)	not reported	2.3% vs.0.5%; 7 vs. 1 deaths	Cohen, 2007 [35]