The Risk of Bleeding in Patients Receiving Therapeutic Anticoagulation and Antiangiogenic Therapy

Vanessa Pachón Olmos1, Virginia Martínez Marín2, Lara Iglesias Docampo3 and Andrés J. Muñoz Martín4; The SEOM Cancer and Thrombosis Working Group

1Department of Medical Oncology, Hospital Universitario Ramón y Cajal, Madrid, Spain; 2Department of Medical Oncology, Hospital Universitario La Paz, Madrid, Spain; 3Department of Medical Oncology, Hospital Universitario 12 de Octubre, Madrid, Spain; 4Department of Medical Oncology, Hospital General Universitario Gregorio Marañón, Madrid, Spain

Abstract

The use of antiangiogenic drugs is increasingly common and bleeding is one side effect. However, cancer patients have a high incidence of venous thromboembolism, which requires treatment with anticoagulation medication and raises the risk of bleeding. In this article, we review the literature on the risk of bleeding in patients treated with anticoagulants and antiangiogenic drugs. Although studies are scarce and have methodological limitations, the data suggest that the combination of both treatments does not significantly increase the risk of bleeding. (Cancer & Chemotherapy Rev. 2012;7:78-82)

Corresponding author: Vanessa Pachón Olmos, li_tor@hotmail.com

Key issues

- Thromboembolic events are very usual in cancer patients.
- Antiangiogenic drugs play an important role in cancer therapies nowadays.
- Literature suggests that the combination of anticoagulation and antiangiogenic drugs is safe enough.
- However, data are retrospective and more investigation is needed.

Introduction

The use of antiangiogenic medication is a new therapeutic method. Recently, many drugs in this family have been used to treat various types of malignancies. Of these drugs, three are the most widely used: bevacizumab, sorafenib, and sunitinib. Bevacizumab is a recombinant humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF). It was the first antiangiogenic agent approved by the FDA in February 2004 for the first-line treatment of metastatic colorectal cancer (mCRC) in combination with fluoropyrimidines1.2. Likewise, its use is approved in advanced renal cell carcinoma (RCC) in combination...
with interferon-α-2a as in the first-line treatment for non-squamous non-small cell lung cancer (NSCLC) and, as well, in combination with paclitaxel or capecitabine in breast cancer. More recently, the FDA has approved its use in glioblastoma multiforme.

Sorafenib and sunitinib are multi-kinase inhibitors acting on the vascular endothelial growth factor receptor (VEGFR) in the tyrosine kinase domain. Sorafenib is approved as monotherapy in patients with advanced RCC and hepatocellular carcinoma. Sunitinib is indicated, also as monotherapy, for advanced RCC, gastrointestinal stromal tumors and neuroendocrine tumors.

As with bevacizumab, there are currently several clinical studies evaluating the efficacy of sorafenib and sunitinib in other tumor types.

The adverse effect profile of antiangiogenic therapy differs from conventional chemotherapy (CT). Given the important role of the VEGF pathway in vascular function, physiological angiogenesis, and the tumor microenvironment, antiangiogenics have been associated with bleeding in clinical trials and clinical case reviews. Most reported cases of bleeding have been mild to moderate; however, there has been reported cases of severe hemorrhage (grade ≥ 3), especially involving the gastrointestinal system, genitourinary tract, and central nervous system. A phase II trial of patients with NSCLC revealed a fatal hemoptysis rate of 9%, especially in those with a squamous histology. This finding led to the exclusion of patients with a squamous histology in a pivotal study of bevacizumab in NSCLC. In the meta-analysis study by Hapani, et al., a relative risk (RR) of bleeding due to the global use of bevacizumab was found to be 2.48 (95% CI: 1.93-3.18; p < 0.001), and the RR was 1.91 (95% CI: 1.36-2.68; p = 0.003) for severe hemorrhage and 3.56 (95% CI: 1.71-7.41; p = 0.001) for fatal bleeding. It should be noted that in the meta-analysis, patients who used > 325 mg daily of aspirin, nonsteroidal anti-inflammatory drugs, or oral or intravenous anticoagulants (with the exception for the prophylaxis of catheters) were excluded.

A meta-analysis has been published examining the risk of bleeding and the increasingly frequent use of inhibitors of tyrosine kinase domain of the VEGFR. It investigated the incidence and relative risk of bleeding in patients treated with sorafenib and sunitinib. Approximately 23 clinical trials were selected out of 275 potentially relevant clinical trials: four phase III (two with sorafenib and two with sunitinib), 19 phase II or expanded use (10 with sorafenib and nine with sunitinib) in various primary tumors. A total of 6,779 patients were obtained for analysis. The results yielded a RR of bleeding of 2.0 (95% CI: 1.14-3.49; p = 0.015) and a RR of severe hemorrhage of 1.16 (0.70-1.92; p = 0.555). There was no difference between sorafenib and sunitinib in the overall incidence of bleeding and severe bleeding. These data come from a retrospective review with small numbers of serious bleeding events and heterogeneity in the reporting of adverse effects.

Alternatively, venous thromboembolic events (VTE) are common in cancer patients, with low-molecular-weight heparins (LMWH) being the treatment of choice. However, it has been reported that the bleeding complications in cancer patients receiving therapeutic anticoagulation therapy are higher, reaching a rate of 13.3 per 100 person-years of severe hemorrhage versus 1.1 in patients without cancer, the difference being statistically significant (p = 0.002). These data must be considered when evaluating the risk of bleeding with antiangiogenesis and anticoagulant therapy.

This article reviews the literature related to the risk of bleeding from the use of anticoagulant therapy and antiangiogenics.

Materials and Methods

We conducted a systematic search of the PubMed database, initially not restricting the publication type, year, or language. In the second step, we eliminated the clinical cases.

The sources of information came from three types of publications: observational studies (three), clinical trials (three) and a meta-analysis study (one) (Tables 1-7). The clinical trials that allowed the concomitant use of anticoagulant therapy and antiangiogenesis are scarce.

Results

We selected three observational studies. The BRITET study is a major prospective, observational, cohort study of 1,953 patients with mCRC receiving first-line treatment of bevacizumab and CT in 248 U.S. centers. The main objective of this study was to assess the safety and effectiveness of adding bevacizumab to CT in clinical practice. Patients were allowed treatment with low doses of aspirin and/or anticoagulant therapy. With a median follow up of 20.1 months, the incidence of severe hemorrhage in patients not on anticoagulant therapy was 2.2%, mostly occurring in the gastrointestinal system. A multivariate analysis was performed of all the baseline characteristics of patients and did not find any statistically significant risk factors for severe hemorrhage.

Approximately 6.8% of the patients received concomitant doses of bevacizumab, anticoagulant therapy, and CT, and severe hemorrhage occurred in 6% of this group of patients.
The BEAT\textsuperscript{23} study is an observational study of patients with mCRC receiving first-line CT with bevacizumab. This study was conducted outside the USA and enrolled a total of 1,914 patients. The main objective was to assess the safety of the combination and secondary endpoints of progression-free survival and overall survival. Patients were allowed treatment with low doses of prophylactic aspirin or anticoagulants in their catheters, and a small proportion of patients started anticoagulant therapy during the study. With a median follow-up time of 21.1 months, 15% of all patients received anticoagulant therapy at some point during the study. The incidence of severe hemorrhage was 4.3% in this subgroup of patients compared to 2.4% in the group of patients who did not receive anticoagulant therapy.

Recently, a study has been published\textsuperscript{24} that retrospectively reviewed 64 cases of gliomas treated with bevacizumab and anticoagulant therapy. The incidence of severe hemorrhage was 6% in the patient group treated with bevacizumab and anticoagulant therapy versus 1% in the patient group treated only with bevacizumab (n = 218; p = 0.03).

The clinical trials that allowed patients to receive anticoagulant therapy and bevacizumab are the following:

The AVADO\textsuperscript{25} study is a phase III study of metastatic breast cancer in which 730 patients received first-line docetaxel with or without bevacizumab. Seven patients in the bevacizumab arm received anticoagulant therapy before entering the study, and 52 were initiated during the same period.

### Tables 1-7. Characteristics of the analyzed studies

AT: anticoagulant therapy.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>(n)</th>
<th>Patients with AT (n)</th>
<th>Risk severe hemorrhage (no AT vs. AT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flynn, et al. 2007</td>
<td>Observational prospective cohorts</td>
<td>1,953</td>
<td>133</td>
<td>2.2 vs. 6.0%</td>
</tr>
<tr>
<td>Van Cutsem, et al. 2010</td>
<td>Observational prospective cohorts</td>
<td>1,914</td>
<td>287</td>
<td>2.4 vs. 4.3%</td>
</tr>
<tr>
<td>Norden, et al. 2011</td>
<td>Observational retrospective cohorts</td>
<td>218</td>
<td>64</td>
<td>1 vs. 6% (p = 0.03)</td>
</tr>
<tr>
<td>Wardley, et al. 2008</td>
<td>Clinical trial</td>
<td>730</td>
<td>59</td>
<td>0%</td>
</tr>
<tr>
<td>Crino, et al. 2010</td>
<td>Clinical trial</td>
<td>1,065</td>
<td>160</td>
<td>4% (no data in AT)</td>
</tr>
<tr>
<td>Friedman, et al. 2009</td>
<td>Clinical trial</td>
<td>167</td>
<td>38</td>
<td>2.5% (no data in AT)</td>
</tr>
<tr>
<td>Leigh, et al. 2011</td>
<td>Meta-analysis</td>
<td>3,201</td>
<td>123</td>
<td>4.1 vs. 4%</td>
</tr>
</tbody>
</table>
without severe hemorrhage being observed during the study.

The SAiL26 project is a phase IV study developed in 40 international centers in which 1,065 patients with NSCLC were recruited to investigate the safe use of bevacizumab. Approximately 15% of patients received anticoagulant therapy (most LMWH), and there was a 4% incidence of severe hemorrhage. The incidence of severe pulmonary hemorrhage was 1%.

Another randomized study of high-grade gliomas27 evaluated the safety of the use of bevacizumab in 167 patients. Anticoagulant therapy was allowed at baseline (22.8% of the population). A 2.5% incidence of severe hemorrhage in the study population was reported, with an intracranial hemorrhage rate of 1.3%. Of the five patients who developed intracranial hemorrhage, two had received anticoagulant therapy.

Finally, a recent meta-analysis28 reviewed three phase III studies, including two studies of patients with mCRC and one study of patients with non-squamous NSCLC, in which bevacizumab was administered and the patients were able to receive concomitant anticoagulant therapy. Patients were excluded from all three studies based on the following conditions: those who had received anticoagulant therapy at baseline, those who used aspirin > 325 mg daily, those who had a bleeding diathesis, or those with cardiovascular disease in the previous year. Patients were also excluded if they suffered VTE that required anticoagulant therapy during the study, with the exception being in cases where there was no evidence of bleeding and in cases decided at the discretion of the investigator. In those cases, anticoagulant therapy was required for a minimum of 2-3 weeks. Prophylactic anticoagulation was allowed to maintain the central lines. In these studies, the most widely used anticoagulant was warfarin. Among the three studies, a total of 123 patients continued being treated with bevacizumab after experiencing VTE. The incidence of severe hemorrhage was similar in the control and the experimental groups. Among the three studies, the estimated overall risk of severe bleeding was 4.1% in the group of patients with bevacizumab versus 4.2% in the control group. The 123 patients treated with bevacizumab and anticoagulant therapy showed an incidence of 4% of severe hemorrhage, and some of these patients presented confounding factors such as thrombocytopenia. There were no cases of fatal hemorrhage in this subgroup. The overall hazard ratio for severe hemorrhage were 9.0 per 100 patient-years with the use of bevacizumab compared to 10.5 per 100 patient-years in the control arm, which are lower than those described in the literature for cancer patients with anticoagulant therapy.

Discussion

In this article, we reviewed the literature regarding the risk of bleeding due to the use of antiangiogenic drugs in patients being treated with anticoagulant therapy. Most of the available information comes from the use of bevacizumab.

It is known that bevacizumab has been associated with an increased risk of bleeding. Although most of these events are epistaxis and other self-limiting bleedings, there have also been cases of severe hemorrhage. In the clinical trials, there was a 3.3-5% incidence of grade 3-4 bleeding; however, it should be noted that these findings are limited by the fact that the clinical trials excluded patients receiving anticoagulant therapy or doses of aspirin higher than 325 mg daily. In two recent meta-analyses13,15, bevacizumab was associated with an increased risk of severe hemorrhage (RR: 1.91; 95% CI: 1.36-2.68; p = 0.003) and of fatal bleeding (RR: 2.77; 95% CI: 1.07-7.16; p = 0.04). Another meta-analysis16 demonstrated a 2.0 RR for severe hemorrhage (95% CI: 1.14-3.49) due to the use of sorafenib and sunitinib.

Alternatively, VTE is very common in cancer patients, and anticoagulant therapy is indicated for treatment; however, bleeding complications are higher than in non-cancer patients18,19.

Our literature review yielded three types of sources: observational studies, clinical trials, and meta-analyses. Observational studies included the BRiTE22 and the BEAT23 studies, in which the use of anticoagulant therapy was allowed. In patients receiving bevacizumab and anticoagulant therapy, the incidence of severe hemorrhage was 6.0 and 4.3%, respectively. However, these two studies were nonrandomized, the subgroup analysis was not provided, and the data regarding concomitant antiplatelet medication use was not properly collected. Also included were the results of an observational retrospective study24 of gliomas in which the incidence of severe hemorrhage significantly increased. The limitations of this study included its small sample size and its retrospective nature.

We collected three clinical trials25,26,27 in which a small proportion of patients received anticoagulant therapy and concomitant bevacizumab. None of the studies specified the incidence of bleeding in this subgroup, although no apparent increase in the incidence of severe hemorrhage with the use of anticoagulant therapy over the expected risk for bevacizumab occurred. The limitations are the small number of patients with combined use of bevacizumab and anticoagulant therapy. In addition, the inclusion criteria of clinical trials tend to exclude elderly patients and patients with cardiovascular comorbidities that may increase the risk of bleeding.
Finally, we reviewed the meta-analysis of Leighl, et al., which included data from three clinical trials, and concluded that the risk of bleeding because of the combined use of bevacizumab and anticoagulant therapy is not higher than the risk associated with the use of anticoagulant therapy alone. However, the subanalysis of patients with VTE is limited by the small sample size. Between 13 and 53% of patients remained in the studies after developing VTE. The reporting of the continuity and duration of the co-incidence of bevacizumab and anticoagulant therapy was at the discretion of the researcher.

Limitations of our literature review included the arbitrary collection of data on the anticoagulant therapy used in the studies (the dose, frequency and duration), and the heterogeneity in the documentation of the adverse effects in the studies.

Conclusions

Antiangiogenic drugs are being increasingly administered to cancer patients, and VTE are occurring with greater frequency among cancer patients, for which anticoagulant therapy is indicated. Although experience is limited, and data has been obtained from subanalyses with key limitations, the literature suggests that anticoagulant therapy can be combined with antiangiogenic treatment without significantly increasing the risk of bleeding that would be expected by the separate use of anticoagulant treatment and anticoagulant therapy. Of course, it is necessary to design prospective studies to corroborate these findings.

References
