Low-Dose Warfarin Prophylaxis for Catheter-Associated Thrombosis in Cancer Patients. Can It Be Safely Associated with 5-Fluorouracil-Based Chemotherapy?

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We read with great interest the article by Dr. Kuter on the complications of central venous catheters (CVCs) in cancer patients [1]. The author describes the mechanism of thrombosis in catheters, explains the symptoms, signs, and sequelae of CVC thrombosis, and discusses systemic anticoagulation prophylaxis to reduce thrombosis. With regard to the latter, based on the literature, the author reports the failure of thrombosis prophylaxis with low-molecular-weight heparin and the controversial role of low-dose warfarin prophylaxis. However, he concludes that minidose warfarin may be a low-risk treatment in well-nourished patients with adequate hepatic function and that it is an open question if there is need for monitoring these patients. Since 1999, after the studies of Bern et al. [2] and Levine et al. [3], we have been prophylaxing cancer patients with CVCs with minidoses of warfarin. However, on the basis of reports describing cases of adverse interactions between warfarin and chemotherapeutic agents, particularly 5-fluorouracil (5-FU), we measure prothrombin time and International Normalized Ratio (INR) at baseline (CVC insertion) and, subsequently, after 2 or 4 cycles of the chemotherapy program [4].

In a first study in 95 consecutive cancer patients, we observed that the combination of minidose warfarin and continuous-infusion 5-FU-based regimens resulted in INR elevations in 33% of patients and that eight patients developed bleeding problems, seven of them with elevated INRs [5]. Furthermore, in patients treated with the combination of 5-FU, folinic acid (FA), and oxaliplatin (Eloxatin®; Sanofi-Synthelabo Inc.; New York, NY), the FOLFOX regimen (oxaliplatin: 85 mg/m² as a 2-hour i.v. infusion on day 1; FA: 100 mg/m² as a 2-hour i.v. infusion on days 1 and 2; 5-FU: 400 mg/m² as a short infusion on days 1 and 2; 5-FU 600 mg/m² as a 22-hour i.v. continuous infusion on days 1 and 2), we observed a significantly higher incidence of INR elevation (p = 0.041) than in patients treated with other regimens. This last observation was confirmed in another study [6] on a large series of patients treated with the FOLFOX regimen, where INR elevation ranging from 1.55-9.4 (mean 3.22) was observed in 25 of 50 patients (50%). Of these, four (8%) had INRs ≥3.0 but < 6.0 and four (8%) had INRs ≥6.0. In both studies, no relationships were observed between liver metastases, hepatic function, age, performance status, number of previous chemotherapy regimens administered, or chemotherapy toxicity and INR alteration or bleeding. Warfarin administration was discontinued if the INR was greater than 1.5, and prothrombin time prolongation resolved within 48 hours in all patients. Chemotherapy was continued thereafter without oral anticoagulant prophylaxis, and none of these patients had any further prothrombin time alteration.

In conclusion, our studies revealed a high incidence of INR elevation when minidose warfarin was given along with a 5-FU infusion with or without oxaliplatin, and we strongly suggest that oncologists should be aware of this interaction and should regularly monitor INR levels in these patients.
REFERENCES


