Incidence of venous thromboembolism in breast cancer patients during chemotherapy with vinorelbine, cisplatin, 5-fluorouracil as continuous infusion (ViFuP regimen): Is prophylaxis required?

Cancer patients have an increased risk of venous thromboembolism (VTE). Previous published reports indicated an incidence of cancer-related VTE between 1%-11% [1]. Pathogenesis of VTE is multifactorial depending upon procoagulant activity of tumor cells, procoagulant host-response and upon co-morbidity factors, which involve vascular damage. Moreover, chemotherapy and endocrine therapy, as well as implanted central venous catheters further increase the incidence of VTE [2, 3].

We retrospectively analyzed the incidence of VTE in 182 consecutive breast cancer patients treated in one institution (European Institute of Oncology) between January 1997 and April 1999 with the ViFuP regimen (Navelbine 20 mg tot i.v. on days 1 and 3, cisplatin 60 mg/m² i.v. on day 1 and 5-fluorouracil (5-FU) 200 mg/m² i.v. daily as continuous infusion) through a permanent central venous device (CVC; Dome Port®, Bard). Seventy-eight patients had early or locally advanced (T1–T2) and 104 patients had metastatic breast cancer. Sixty-one patients (58.6%) in the metastatic group and twenty patients (25%) in the neoadjuvant setting were post-menopausal. Median age was 48 years (range 23–72). All patients had performance status 0–1. In a previous series of 333 patients with a permanent central venous device treated at the same institution we observed a low incidence of symptomatic VTE (1.5%) and therefore we did not consider the use of prophylactic anticoagulation [4]. The median follow-up was 15 months (range 1–27+) for the metastatic group and 8 months (range 1–15+) for the patients treated in the neoadjuvant setting.

We observed 14 episodes of VTE (7.7%; 95% confidence interval (95% CI): 4.3%–12.6%), similarly distributed among patients with overt metastases (8 out of 104 patients, 7.7%; 95% CI: 3.4%–14.6%) and those with early or locally advanced disease (6 out of 78 patients, 7.7%; 95% CI: 2.9%–16%). All patients experienced VTE during chemotherapy. Median time from surgery for implant of central venous device to thrombosis was 2 months (range 1–4 months). Only one woman had a history of previous thromboembolic disease. Two women had VTE of the lower limb and one of them developed pulmonary embolism while all other VTE involved veins next to implantation site. Three patients had no symptoms (21%) and diagnosis was occasionally made during evaluation of response to treatment. After diagnosis of VTE, all patients received five days of low molecular weight heparin at the dose of 100 mg/kg twice a day plus oral warfarin to maintain an INR between 2.0–3.0. Despite maintenance anticoagulation, two patients experienced a new episode of VTE. All patients who had VTE treated in the neoadjuvant setting stopped the chemotherapy and were candidates to surgery.

The incidence of VTE observed in patients receiving the ViFuP regimen is not negligible. Similar incidence of VTE have been reported in breast cancer patients treated with combination chemotherapies in the adjuvant setting and with advanced disease [5]. Weiss reported an incidence of 5%–7% in 433 patients treated with adjuvant cyclophosphamide, methotrexate, and fluorouracil (CMF) [2]. An increased thromboembolism (17%) in stage IV breast cancer treated with CMF and vincristine was also reported [3]. Patients with metastatic disease seemed to be at a higher risk of thrombosis than patients treated in the adjuvant setting, although in our series the incidence of thrombotic events in the two groups was similar.

Limited data are available on the incidence of thrombosis in patients treated with 5-FU as continuous infusion for whom an incidence of VTE ranging from 4%–16% has been described [2].

The issue of antithrombotic prophylaxis in cancer patients was addressed in some randomized studies. Levine et al. demonstrated that very low-dose warfarin decreases the incidence of VTE in metastatic breast cancer patients treated with chemotherapy [5]. The daily use of low dose warfarin (1mg) or low molecular weight heparin (2500 UI) was protective in terms of catheter-related thrombosis in several studies [6, 7], while some reported lack of reduced risk of VTE with these treatments. There is limited information on the preoperative setting, and specifically for regimens delivered as continuous infusion. Smith observed a 10% catheter-related thrombosis in 50 breast cancer patients treated with a neoadjuvant infusion chemotherapy, despite the use of 1 mg of warfarin [8]. The routine use of anticoagulant prophylaxis during continuous infusion of 5-FU is theoretically hampered by a potential interaction between warfarin and this drug. Prolonged 5-FU half-life and increased INR were reported, thought to be due to interference with the synthesis of hepatic cytochrome 450 and impaired metabolism of warfarin and 5-FU [9, 10]. More information is needed on the proper anticoagulant regimen during infusional treatment containing 5-FU.

When comparing this series of 182 patients with the one of 333 patients with implanted CVC for systemic chemotherapy and iv nutrition treated in the same institution without using the ViFuP regimen [4], one may observe a significantly higher incidence of symptomatic VTE (6% vs. 1.5%; P = 0.0019). Moreover, the former study was closed on 30 September 1997, whereas the majority of ViFuP treatments was carried out after this date, until April 1999. This indirect comparison suggests a possible role of the chemotherapy regimen, or one of its components, which might be particularly endothelial damaging. Studies are required to identify the best strategy for avoiding VTE, which is particularly troublesome in the preoperative setting. Further information are needed to determine the impact of newly genetic risk factor for thrombosis, such as prothrombin gene mutation, deficiencies of antithrombin III, protein C or protein S, in order to identify a particular high risk subset of patients for which a thromboprophylaxis should be considered [11].

L. Orlando,1 M. Colleoni,1 F. Nolè,1 R. Biffi,2 A. Rocca,1 G. Curigliano,1 G. Ferretti,1 G. Peruzzotti,1 F. de Braud,1 G. Masci1 & A. Goldhirsch1
1Department of Medical Oncology, European Institute of Oncology. 2Division of General Surgery, European Institute of Oncology, Milan, Italy
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Since the literature on tumor imaging with positron emission tomography (PET) is rapidly expanding, and many clinical studies are still being carried out, clinicians are confronted with an enormous amount of data in varying scientific papers. Therefore, a concise overview of the indications for oncologic PET imaging is certainly needed.

The present work consists of two parts. Part I is divided into three main chapters discussing first: physical principles with respect to PET and dual head coincidence camera technology, the physics of positrons, and quality control. The second chapter deals with radio-pharmaceutical technology, toxicity and radiation dosages of 18F FDG, and the third with metabolism and the transport of glucose and 18F FDG. These chapters are well written and comprise an excellent overview. Chapters 1 and 2 are short and concise, but Chapter 3 is too detailed for referring physicians who are, according to the editors, the main target of this book.

Part II deals with clinical aspects of PET imaging, and again, can be divided into three main sections. The first two chapters describe patient preparation, the PET scanning technique and the current clinical indications for PET imaging. These are also well written and concise. However, the PET imaging protocols are only one proposal and the reader should be aware that scanning protocols may be substantially different in other institutions. Moreover, the definition of a whole-body PET scan is somewhat confusing, as the authors are defining a whole-body scan from the base of the skull to the upper third of the thighs. In other institutions, a whole-body scan is defined differently, namely, from the top of the brain to the toes.

The largest part of the present work is dedicated to the clinical indications for 18F FDG PET imaging. Discussed are malignant melanoma, head & neck tumors, thyroid carcinoma, pulmonary nodules and non-small-cell bronchial carcinoma, breast, pancreatic, colorectal, ovarian and testicular cancers, Hodgkin's disease and non-Hodgkin's lymphomas, brain tumors, and, finally, miscellaneous tumors. The chapters start with the therapeutic possibilities and end with the indications for PET scanning. The most important clinical papers dealing with PET imaging are discussed as well as the comparative studies with other imaging modalities. In most chapters, the overview is excellent, short and very informative, the literature review sufficient. Unfortunately, the very informative current classification for the clinical use of 18F FDG PET imaging (consensus conference, Ulm, 1997) is not included in all chapters.

The book ends with information regarding cancer screening with whole body PET, PET and radiotherapy and the cost effectiveness of FDG PET.

In general, the book offers an up-to-date review of the current clinically useful indications for oncologic PET imaging. It is very well written, the image quality is good to excellent and it provides a great deal of of information, not only for referring clinicians but also for practitioners of nuclear medicine. It can indeed be recommended to referring physicians because it certainly facilitates making the decision of whether or not to refer a patient for a PET study.

I. Engel-Bicik
Zurich