Video meliora proboque sed deteriora sequor: the case of thromboprophylaxis in hospitalized cancer patients

Publio Ovidio Naso was a Latin poet and had a deep knowledge of the human mind. To describe the human natural inclination to make mistakes, he wrote the famous phrase: ‘I see the best way and approve it, but I follow the worse one’ (video meliora proboque sed deteriora sequor).

This ancient statement might apply as well to the current clinical management of venous thromboembolism (VTE) in cancer patients, and, who knows, Ovidio was also referring to the natural propensity of Latin doctors to ignore the potential dramatic problem of VTE complication. He never would have thought that this error would persist prolonged till our days!

The history of VTE and cancer begins with Trousseau in 1865 when he first described the high incidence of VTE in patients with gastrointestinal carcinoma. Thereafter it has been extensively recognized that VTE is a common complication of patients with malignancy [1].

VTE is a major public health issue [2] and one of the most important causes of morbidity and mortality in cancer patients with negative impact on their quality of life [3]. It has been estimated that VTE is the second leading cause of death in hospitalized and ambulatory cancer patients [4].

Since VTE is a multifactorial event, the absolute risk depends on several factors including: tumor type, stage of disease, the administration of chemotherapy and/or hormone therapy, surgical interventions, length of anasthesia, the presence of indwelling central venous catheters, age, immobilization and previous history of VTE [5]. The increased risk of recurrent VTE in cancer patients is greatest in the first few months after the malignancy is diagnosed [6] and can persist for many years after an initial episode of symptomatic VTE. While receiving chemotherapy, cancer patients have a seven-fold risk to develop VTE as compared with other patients without cancer.

Hospitalized cancer patients are at an even higher risk of developing VTE. In a recent retrospective study involving >66,000 adults with cancer, 5.4% of patients developed VTE during the 8 years of the study [7]. Furthermore, in a retrospective study, cancer patients were found to have a three-fold higher risk for recurrent VTE than patients who had an initial VTE in the absence of malignancy [8]. The probability of readmission for recurrent VTE within 183 days was 22% for cancer patients compared with 6.5% for those without malignancy [8].

Since active cancer, hospitalization, immobilization and chemotherapy increase dramatically the risk for VTE, one may argue that medical oncologists should make all efforts to reduce this complication by adopting pharmacological and mechanical prophylaxis.

In this issue of the journal, Kucher et al. [9] explored clinical predictors of appropriate mechanical or pharmacological prophylaxis among medical and surgical patients who suffered acute VTE during or shortly after a hospitalization. To do this the authors evaluated clinical data of 257 cancer patients with acute VTE relative to prior hospitalization for acute medical illness or surgery within 30 days preceding an acute VTE event. All patients were prospectively enrolled in the Swiss Venous Thromboembolism Registry. Prophylaxis treatment was judged appropriate according to the recommendations from the American College of Chest Physicians (ACCP) 2004 [10].

This study was not specifically dedicated to cancer patients, but cancer patients represented 45.3% of the total studied population. Unfortunately, we missed important details including neutropenia (and granulocyte colony stimulating factors), anemia (and possibly concomitant erythropoietin treatment), the tumor histotype and the cytotoxic treatment including the use of antiangiogenic agents.

Finally it is not reported which percentage of the total cancer population is concerned, so that we cannot assume the scale of the problem in oncological patients.

The first important result of the study is that only 60% of patients had received prophylaxis, which means that 40% of hospitalized cancer patients at high risk to develop VTE actually did not receive any prophylaxis. Furthermore, among the 144 medical patients, only 48% received prophylaxis as compared with 74% of surgical patients.

The increased use of prophylaxis in surgical cancer patients may be easily explained since it is well known that the benefits of prophylaxis in the surgical setting have been accepted for many years. On the contrary, evidence of benefits in medical patients has been produced more recently and therefore awareness for VTE risk may be lower in this population.

It is worth to underline that none of very important VTE risk factors, such as age, obesity, metastatic disease, acute heart and respiratory failure and infections, were predictive for prophylaxis.

These results are consistent with those reported from the multinational International Medical Prevention Registry on Venous Thromboembolism and the Spanish Registro Informatizado de la Enfermedad Tromboembólica registries [11, 12].

Recently Cohen et al. [13] carried out a multinational cross-sectional survey designed to assess the prevalence of VTE risk in the acute care setting and to determine the proportion of at-risk patients who receive effective prophylaxis. Among medical patients judged to be at high risk according to the ACCP 2004...
evidence-based consensus guidelines, only 41.5% of medical patients received prophylaxis and within that group of medical patients, 37% of cancer patients received prophylaxis.

In summary, all these studies demonstrate a dramatic scenario in the oncological world and are an important reminder that there is a definite need to improve prophylaxis in hospitalized cancer patients.

The study by Kucher et al. [9] reported that the most common reason for inappropriate prophylaxis (40% of all discharges) was no prophylaxis at all, despite having no contraindication to anticoagulation. Among the 104 patients without prophylaxis, 88 had a Geneva VTE risk score ≥3, which means the presence of important comorbidities or immobilization in addition to the presence of cancer. These are important data because it is well known that the incidence of VTE increases in relation to the number of patient’s risk factors.

Now the question is why this potential fatal complication is so largely underestimated?

Clinical trials are important to better understand the clinical course of a disease, to improve treatment, and to reduce the suffering of cancer patients. In order to bring attention to a specific toxicity and to raise the awareness about it, it is extremely important that such a toxicity is reported with details: this is the first step to the knowledge. As stated by Greek and Latin scientists ‘nihil is in intellectu quid prius not fuerit in sensu’: Nothing is in the mind that was not before in the senses, which means ‘we cannot think about a problem if we do not experience it’.

What is happening in medical oncology?

One of the most important scales of toxicity reported in clinical trials is the National Cancer Institute Common Toxicity Criteria (NCICTC). In the initial version of the NCICTC scale, VTE was not included in the table of toxic effects. Furthermore, the current toxicity definitions with respect to VTE are poor and need clarification.

No differences, e.g. are highlighted between proximal venous thrombosis and distal venous thrombosis (DVT), although patients with DVT of the calf have about half the risk of recurrent VTE as those who have had a proximal DVT.

Furthermore, the risk to develop pulmonary embolism is increased for patients with proximal DVT as compared with those with distal DVT. In the third version of the NCICTC scale grade 2 and grade 3 are strictly related to the need of a therapeutic approach, but there are often clinical situations in medical oncology, where the decision to administer antithrombotic treatment is made very difficult by thrombocytopenia or other transient medical conditions.

In addition, no mention is highlighted regarding the fact that in several cases venous thrombosis is a clinically asymptomatic event.

Our group recently reported the incidence and the underestimation of VTE in advanced colorectal cancer patients within the Italian Group for the Study of Digestive Tract Cancer alternating-schedule study [14].

If we run an extensive Medline and Cancerlit review (2004/2007) to retrieve the reported VTE events in randomized clinical trials investigating the role of a first-line chemotherapy in advanced colorectal cancer patients, we will find that only 1 of 28 randomized clinical trials reported VTE complication in the table of toxic effects. Of course, these findings could also be extended to other common solid tumors.

It may be useful to remember that until 2 years ago no clinical recommendations were produced about VTE by the oncological community. The lack of recommendation sets well the scene regarding the underestimation of this type of toxicity as compared with other toxic effects such as nausea, vomiting and anemia.

Since VTE was not considered as a relevant issue, no specific study has been carried out in hospitalized cancer patients by the oncology community. Fortunately, in the meantime, three large, high-quality clinical trials, in hospitalized ‘medical patients’, which included cancer patients, have demonstrated that prophylaxis leads to a lower VTE incidence compared with placebo, without increasing major bleeding [15–17].

The study populations in these trials only included 10%–15% of patients with cancer. On the basis of these results in the ‘medical setting’, the American Society of Clinical Oncology, the European Society of Medical Oncology, the National Comprehensive Cancer Network and the ACCP strongly recommended pharmacological prophylaxis in the absence of contraindication (Recommendation IA) [18–20].

The low bleeding rates observed with low molecular weight heparin and Fondaparinux prophylaxis in the three major medical trials strongly support for safety of thromboprophylaxis in hospitalized cancer patients [15–17]. One potential caveat may be that none of these studies published bleeding rates specifically for the cancer subgroups of their populations.

Although these recommendations are based on clinical trials that included only a minority of patients with cancer, considering the morbidity and mortality from VTE, in the real world we must consider that it will be difficult to design future randomized trials in hospitalized cancer patients with a control group receiving no prophylaxis or placebo. Future prospective observational studies may help to better define the VTE and the bleeding risks in specific subgroups of hospitalized cancer patients. Another important issue is what is the optimal duration of thromboprophylaxis in medical cancer patients?

Many medical patients have severe comorbidities, including immobilization and acute illness, before and after hospitalization. It is logical to think that the thrombotic process may already have started before or will continue after hospitalization. This means that many patients, before hospitalization and after discharge, may actually need prophylaxis, although no current guidelines recommend prophylaxis for ambulatory cancer patients with solid tumors and ongoing chemotherapy.

This represents a challenge, because these clinical situations have not been scientifically evaluated in clinical trials. VTE is a dynamic process and patients should be monitored every day in order to make a fair decision for thromboprophylaxis. Kucher et al. reported that almost one-quarter (23%) of patients developed VTE as outpatients shortly after hospitalization and raise the question of thromboprophylaxis in outpatients at risk for VTE. Future studies are needed to clarify this important issue.
Considering that general and cancer-specific recommendations for prophylaxis have been published, how to implement the prophylaxis rate in hospitalized cancer patients? Publication of guidelines for thromboprophylaxis, by itself, is only a first step but it is not enough. Several strategies may be adopted in order to reduce the VTE burden.

In a previous study by Kucher et al. the implementation of a computer-alert program increased physicians’ use of prophylaxis and markedly reduced the rates of VTE among hospitalized patients at risk [21]. However, not all hospitals are able to use this electronic device especially outside tertiary and university teaching and academic hospitals.

One of best strategies is an integrated multiple-intervention approach, which may include education and decision support tools such as a pocket card which summarizes the thromboprophylactic options in patients at VTE risk; furthermore, it would be useful to stimulate, also through Web site, a multidisciplinary approach to prevent VTE (e.g. www.coalitionstopreventVTE.com). Most importantly, it would be desirable to introduce a regular audit by the chiefs of the medical and oncological departments and other clinical authorities within the quality process programs.

Finally we need an intensive collaboration between the oncologists, the hematologists, the internists and family doctors. The goal is to adapt the current guidelines to specific regional and local situations and then work together to grow the seed in the best ground.

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