gests that chemoattraction to these areas takes place, possibly through a network of cyto- and chemokines (and their cognate receptors on bone marrow cells) which can be released by the damaged heart. We do not yet know which molecules and receptors drive bone marrow cells to the infarcted areas, but recently we have learnt how the SDF-1/CXCR4 axis plays a pivotal role in the mobilization of hematopoietic stem cells from the bone marrow to periphery and in homing after transplantation.[17] It is possible to envisage a similar mechanism for the migration of bone marrow mononuclear cells to the infarcted heart. If, in coming years, the scientific community can clarify the real contribution of (hematopoietic) stem cells to the repair of damaged myocardium and identify the molecules that regulate their migration, then we really will be close to the possibility of curing myocardial infarction in human patients through a simple injection of bone marrow cells into a peripheral vein, as the study by Ciulla and colleagues so tantalizingly suggests.

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Thrombosis and malignancy: an underestimated problem

Malignancy is a thrombophilic condition and there is clinical evidence that patients with cancer have a significantly increased risk of thrombosis. The pathogenesis is multifactorial and, in great part, relies on the capacity of tumor cells to interact with the hemostatic system and activate it in several ways. The association between cancer and thrombosis is clinically relevant because, on the one hand, thrombosis can represent the first symptom of an occult cancer and, on the other hand, thrombotic events in patients with a known malignancy can influence the morbidity and mortality of the underlying disease. Furthermore, it is important to be aware that many factors, such as surgery and chemotherapy, may increase the thrombotic risk in cancer patients. Recently, a number of strategies for prevention and management of thrombosis in cancer have been under evaluation.

The association between cancer and venous thromboembolism (VTE) has been known for over a hundred years. Since the beginning, this association appeared to have a dual significance. First, there is the concept that the occurrence of VTE is a common complication of cancer, as underlined by Armand Trousseau in 1865, who observed that «*in cancer there is a special condition of the blood predisposed to spontaneous coagulation even in the absence of inflammatory reactions*».[1] Second, the possibility of a relation between the clotting mechanism and the development of metastases was postulated as early as 1878 by Billroth, who described cancer cells within a thrombus and interpreted his finding as evidence of the spread of tumor cells by thromboemboli.[2] We here focus our attention mainly on the first aspect.

The mechanisms of thrombus promotion in malignancy include some general host responses to the tumor (acute-phase, inflammation, angiogenesis,

etc.) and specific interactions of tumor cells with the clotting/fibrinolysis systems and with blood (leukocytes, platelets) or vascular cells.[3] It is at present difficult to rank the relative weight of these multiple interactions on the risk of clinically overt thrombosis in cancer patients. Moreover, the mechanisms explored so far offer a sound experimental basis to support and explain the hypercoagulable state associated with malignancy.

The wide spectrum of manifestations of the prothrombotic state in cancer ranges from an asymptomatic condition, characterized by abnormal plasma coagulation tests, to massive thromboembolism, when the patient may be seriously ill. Although, deep vein thrombosis (DVT) of the lower limbs is the commonest clinical manifestation in cancer patients, DVT of upper limbs, pulmonary embolism, central sinus thrombosis, migratory superficial thrombophlebitis, as well as syndromes with more systemic involvement of the clotting system, such as disseminated intravascular coagulation or thrombotic microangiopathy, have all been described.

VTE is an important cause of morbidity in patients with malignant disease, but an exact appreciation of the magnitude of the problem of VTE in cancer is not easy. Much of the early information comes from small series, or retrospective analyses, or *post-mortem* studies. Our understanding of the epidemiology of VTE in cancer has only recently become clearer with the advent of large population-based studies, and the data from prospective series describing outcome with regard to VTE. Weighing the magnitude of the problem of VTE in cancer, its relationship to various therapeutic interventions, stage of disease and site of origin of the primary tumor is essential in order to develop strategies to prevent these complications.

Current epidemiological data can help us to address the following questions in patients with cancer and VTE: i) what is the probability of occult cancer in patients with idiopathic or secondary VTE; ii) what is the risk of thrombosis in patients with known cancer and selected conditions; iii) what is the risk of recurrent VTE in cancer patients and in non-cancer patients.

Occult cancer in patients with VTE

The probability of a new diagnosis of cancer within 6-12 months of the diagnosis of idiopathic VTE (including pulmonary embolism) is well supported by retrospective analyses of large numbers of unselected patients, population-based retrospective cohort analyses from large registries and prospective studies. The odds ratios for a new diagnosis of cancer in these studies are in the range of a 4-7 fold increased risk.

Retrospective studies have shown a rather consistent pattern of a significant difference in the incidence of cancer between patients with secondary VTE (1.8-7.1%) and those with idiopathic VTE (6.5-16.6%).[4] Two very large, retrospective, population-based studies published in 1998 demonstrated that the incidence of cancer was increased during the first year following the diagnosis of VTE, and that this effect persisted for up to 10 years.[4]

Retrospective studies, however, pose several problems. In particular, it is difficult to determine from registry data whether objective criteria were utilized for the diagnosis of VTE and to find the data supporting the distinction between primary (or idiopathic) VTE and secondary VTE. Furthermore, documentation of other risk factors (such as congenital thrombophilia, pregnancy, use of oral contraceptives, obesity) is frequently missing, as is the information that the presence of a concurrent cancer had been carefully excluded by comparable criteria. A selection bias may be present unless consecutive patients were admitted to the study.

Data from well-designed, prospective trials are essential to answer the question of whether the risk for occult cancer is significantly increased in patients with idiopathic VTE. In 1992 Prandoni *et al.*[5] published the results of a study of 145 patients with well-documented idiopathic VTE and 105 patients with equally well-documented secondary VTE, all of whom were followed closely for at least 1 year after the diagnosis of VTE. Eleven of the 145 patients with idiopathic VTE (7.6%) developed cancer within 12 months, whereas 2 of the 105 (1.9%) with secondary VTE did so (p=0.043). Patients with recurrent, idiopathic VTE had an even higher risk of developing cancer.[5] Similar results have been reported in other prospective studies. Schulman and Lindmarker recently provided important corroboration of these findings in another prospective study, albeit with a very different study design.[6]

Thus the question of whether there is an increased risk of occult cancer in patients with well-defined idiopathic VTE clearly has an affirmative answer. A subset question on the likelihood of discovering a tumor in patients with idiopathic VTE has not yet been answered. A prospective, randomized, controlled trial entitled *Screening for Occult Malignancy in Patients with Symptomatic Idiopathic Venous Thromboembolism* (SOMIT), designed to answer this question, has been conducted in Italy and the results are under evaluation.

VTE as a complication of cancer

As already mentioned, the incidence of VTE in cancer patients at *post-mortem* may be as high as 50%. Nevertheless, the optimal study design for determining the true incidence of clinical VTE in cancer patients is a prospective cohort study. In this sense, valuable data are available for selected conditions, i.e. patients exposed to either medical or surgical

treatments for cancer.

A retrospective analysis[7] of data derived from randomized clinical trials of therapy in patients with breast cancer, in which data were collected prospectively, was the first attempt to evaluate this risk prospectively. In this setting of breast cancer, the studies demonstrated that therapy with an estrogen receptor agonist (i.e. tamoxifen), chemotherapy, combination therapies (tamoxifen + chemotherapy), the stage of the disease and the menopausal status significantly (though differently) affect the rates of VTE. The rates escalate rapidly with advancing stage of disease and the use of chemotherapy, both of which probably contribute to the hypercoagulability characteristic of patients with more extensive disease.[7] The reported rate of thrombosis in women with stage II breast cancer on chemotherapy varies between 5 and 13%,[8] with the highest rates of thrombosis observed in postmenopausal women. Chemotherapy plus tamoxifen increases the risk of VTE over that of chemotherapy alone and in one study the rate of thrombosis in patients with metastatic breast cancer receiving chemotherapy was 17.5%.

Other patients with advanced cancers who are likely to be at higher risk of thromboembolism include patients with brain tumors receiving chemotherapy, those with locally recurrent rectal cancer receiving radiation, and those with pancreatic cancer or advanced gastrointestinal cancers (particularly adenocarcinomas).[7] However, precise estimates of thrombotic rates in these groups of patients are not available. Von Templehoff *et al.* reported a 10.6% rate of VTE in women with advanced ovarian cancer receiving chemotherapy. Rates of 24% to 60% have been reported in high grade gliomas, and 5-10% in patients with Hodgkin's or non-Hodgkin's lymphoma.[8] In addition, cancer patients with indwelling central venous catheters are at increased risk of thrombosis of the axillary/subclavian vein,[9] with the catheters themselves being susceptible to thrombotic occlusion despite the use of routine heparin flushes.

Surgical intervention in patients with cancer increases the risk of postoperative VTE (approximately two fold) in comparison to the risk in non-cancer patients undergoing the same procedures.[10] The risk of VTE in cancer patients undergoing specific types of surgery can be derived from the *no treatment* control arms of trials evaluating prophylaxis of VTE in surgery. Subset analysis has been used, since cancer patients usually constitute approximately 20% of the patients in these studies. The approximate rates for VTE were: general surgery - 29%; gynecological surgery - 20%; urological surgery - 41%; orthopedic surgery - 50-60%; and, neurosurgery - 28%. However, it must be emphasized that many of the thrombi detected were asymptomatic and some of the studies included non-cancer patients, so these rates may not be accurate. Nevertheless, the American College of Chest Physicians has stratified patients with malignancy in the highest risk category of surgical patients and urged routine thromboprophylaxis for these patients.

Turning now to the issue of the distribution of specific cancers associated with thrombotic complications, it appears that the historical association made by Trousseau and others of thrombosis with gastrointestinal tumors, and with carcinoma of the pancreas in particular,[1] has heavily influenced our views of which types of cancers are linked to thrombophilia. A series of case reports from the literature reported that the most common cancers associated with thrombosis were pancreatic, lung, and stomach cancers. Lieberman, in a retrospective series, reported that the most common cancers associated with thrombosis in males were cancers of the lung and pancreas, while the most common neoplasias associated with thrombosis in females were gynecologic, colorectal and pancreatic cancers. It is likely that the distribution of specific cancers associated with thrombosis follows the frequency of the cancer in the general population, which is once again best determined in patients entered into prospective clinical trials of antithrombotic agents, as illustrated by observation in a study by Levine *et al.*[11] The authors evaluated outpatient therapy with low molecular weight heparin for proximal DVT and found that 103 of the 500 patients entered into the study had cancer. The most common anatomic sites for cancer in men were prostate, colorectal, brain and lung and the most common sites in women were breast, ovary and lung. Again we must consider that this type of retrospective analysis of data from studies not designed to assess prospectively the incidence of thrombosis in cancer is not ideal. Nevertheless, the data were collected prospectively and get close to an appropriate answer regarding associations of thrombosis with specific types of cancers.

Recurrent VTE

As for post-operative DVT in cancer surgery, the relative risk for recurrence of VTE in the first 3 months after an initial episode in cancer patients treated with heparin and coumadin is about double that in non-cancer patients.

In a prospective cohort study in 355 consecutive patients with DVT treated with heparin followed by warfarin, the risk of recurrent VTE in the 3-month follow up period was higher in cancer patients (10.3%) than in non-cancer patients (4.7%).[12] Hutten *et al.* recently compared the rates of recurrent VTE and bleeding in cancer and non-cancer patients in two randomized trials which compared low molecular weight heparin with standard unfractionat-

ed heparin for initial treatment of acute venous thromboembolism.[13] The study included 261 patients with malignancy and 1,038 without cancer. The rates of recurrent VTE were 27% per year versus 9% per year, respectively, $p = 0.003$. These data are supported by the results of a recent population-based cohort study, which compared the outcome of anticoagulation courses in 95 patients with malignancy with the outcome of 733 patients without malignancy.[14] The rate of recurrent thrombosis in cancer patients was 6.8% compared to 2.5% in non-cancer patients, $p = 0.06$. An important contribution to this particular aspect has been given very recently by a prospective trial published by Prandoni and colleagues.[15] Clinical trials have been initiated to test alternative anticoagulation strategies for the prevention of recurrent VTE in patients with cancer.

Conclusions

In conclusion, analysis of the literature shows that the risk of occult cancer in patients with idiopathic VTE is approximately 4-7 fold higher, as determined by prospective trials designed to compare the cancer risk in patients with well-defined idiopathic VTE with that in patients with secondary VTE (i.e. due to known causes). This odds ratio rises to perhaps 9 fold when data are examined from patients with *recurrent*, idiopathic VTE. Thus, patients with idiopathic VTE in whom all other causes have been carefully excluded should be followed closely for the development of cancer, particularly during the 6-12 months immediately following the episode of VTE.

It is equally well established that the odds ratio is approximately 2, when comparing the risk for postoperative VTE in cancer patients with that in non-cancer patients undergoing the same surgical procedures, and comparing recurrence of VTE in cancer patients and non-cancer patients.

At present, further studies are needed to collect data prospectively to address the incidence of thrombosis in different types of cancers.

Quantification of the magnitude of the thrombotic risk associated with malignancy and with anticancer interventions is indispensable in order to develop the optimum anticoagulant strategies to protect cancer patients from thromboembolism.

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The treatment of venous thromboembolic disorders: new challenges and opportunities

The aim of treating patients with venous thromboembolism (VTE) is to improve outcomes by preventing extension of the thrombosis, embolization to the lungs, and the development of late complications, such as recurrences, post-thrombotic syndrome, and chronic pulmonary hypertension.

The large majority of patients with VTE are currently treated with full doses of unfractionated (UFH) or low-molecular-weight heparin (LMWH) followed by at least three months of oral anticoagulant therapy.[1] Selected patients with critical manifestations of pulmonary embolism (PE) are administered thrombolytic drugs, while intravenal cava filters are confined to patients with either deep vein thrombosis (DVT) or PE who present with serious contraindications to conventional anticoagulation.[1]

Although considerable progress has been made in the treatment of venous thromboembolic disorders, many unanswered questions remain and await proper solution. Furthermore, new opportunities are