Cancer associated venous thromboembolism

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Summary

Cancer represents a well recognized risk factor for venous thromboembolism. Patients with cancer have a 4-7 fold higher risk for venous thromboembolism than patients without the disease. Some sites of cancer (e.g. pancreas, stomach) are associated with a higher risk than others (e.g. breast, prostate); advanced stage is also associated with a higher risk. Finally, numerous chemotherapeutic agents contribute to the development of venous thromboembolism. Despite the high incidence of thromboembolism, routine primary prophylaxis is not recommended in most cancer patients. Scores that evaluate site, stage and concomitant risk factors are being evaluated but have not gained widespread acceptance to date. Screening patients with venous thromboembolism for occult cancers has shown little impact on survival and in general is not recommended. The pathogenesis of thrombosis in cancer patients, although extremely complex, involves the synthesis of proinflammatory mediators by the host that contributes to the activation of the coagulation cascade, as well as the synthesis of the procoagulant and proangiogenic factor, tissue factor, by the tumor. Patients with venous thromboembolism and active cancer are usually treated with low molecular weight heparin for 6 months; after that, there are no clear guidelines to suggest the best therapeutic approach. The new direct oral anticoagulants are currently not indicated in these patients; however, clinical studies are in progress to evaluate their promising role in this setting.

KEY WORDS: cancer, venous thromboembolism, vitamin K antagonists, low molecular weight heparin, direct oral anticoagulants, tissue factor.

The association of venous thrombosis with cancer was first reported by Jean-Baptiste Bouillaud (1796-1881) and a few years later by Armand Trousseau (1801-1867) (1). The observation has been confirmed countless times and is currently a topic of great and ever increasing interest. The interplays among cancer, anticancer therapies, and venous thrombosis are so complex that VTE in cancer patients might in fact be considered a different disease that warrants different management strategies.

Epidemiology

Numerous studies have attempted to quantify the risk of venous thromboembolism (VTE) in cancer patients. In a recent cohort study using linked UK databases, for example, the incidence of VTE in cancer patients was estimated at around 10 cases/1000 persons/year at the beginning of the survey (1997) and increased steadily to 18/1000 persons/year over the following decade (2). The corresponding figure in the general population remained steady at approximately 3 cases/1000 persons/year. The increase of VTE over time in cancer patients likely reflects the increased survival of patients as well as the increased aggressiveness of anticancer therapies that, as will be discussed later, contribute to the pathogenesis of thrombosis. These figures have proven rather consistent across different studies in different Countries. Accordingly, in a recent review the incidence of VTE in cancer patients was reported to be approximately 4 to 7 fold higher compared to subjects without the disease (3). However, it is also evident that the risk of VTE changes with both type and stage of cancer. The same UK survey previously cited reported an incidence of VTE of nearly 100/1000 persons/year for pancreas cancer compared to, for example, 40 cases for lung cancer and 10 for breast and prostate cancer (2). While the association of some types of cancer (e.g. pancreas, brain, lung) with a particularly high risk of

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VTE is well established, in other cases there is no agreement in the literature; Walker et al., for example, report a particularly low incidence of VTE associated with testicular cancer (3 cases/1000 persons/year, the same value reported for the general population), while in a study specifically aimed at the identification of risk factors for the development of VTE in cancer patients, testicular cancer was classified among the "high risk" types of cancer, together, for example, with lung cancer (4). Finally, not surprisingly, more advanced cancers tend to be associated with higher risks of VTE (5).

Another critical issue in the development of VTE in cancer patients is represented by therapy. In the Olmsted County population study the relative risk of developing VTE was 4.1 in patients not treated with chemotherapy and 6.5 in patients treated with chemotherapy (6). In patients with node-positive, operable breast cancer, the addition of a 6-month course of cyclophosphamide, methotrexate and fluorouracil to the standard regimen including only tamoxifen increased the cumulative incidence of VTE at 2 years from 2.6 to 13.6% (7). Numerous anticancer drugs have specifically been associated with an increased risk of VTE. The list includes cisplatin, thalidomide, vinca alkaloids, fluorouracil, tamoxifen (8). Besides chemotherapeutic agents, other molecules widely used in cancer patients are responsible for an increased risk of VTE. The antivascular endothelial growth factor monoclonal antibody, bevacizumab, is associated with a 33% increase in the risk of VTE. The figure, albeit small, is statistically significant. However, it is important to note that the well documented prothrombotic effect of the molecule is mainly related to arterial thrombosis (relative risk 2) (9). In contrast, the oral anti tyrosine kinase agents, erlotinib and sunitinib, while associated with an even larger increase in the risk for arterial thrombosis (relative risk 3), have not been involved in the pathogenesis of VTE (9). Finally, a 67% increase in the relative risk for VTE has been attributed to erythropoietin (10). Surgery and radiotherapy must also be included among the risk factors for VTE in cancer patients (9). Table 1 summarizes the principal highlights about the principal epidemiologic data regarding VTE in cancer patients.

Table 1 - Highlights on the principal epidemiologic data regarding VTE in cancer patients.

- Patients with cancer have a 4-7 fold higher risk of venous thromboembolism compared to the general population.
- Some cancer sites (e.g. pancreas, stomach) are associated with a higher risk than others (e.g. prostate, breast).
- More advanced stages are associated with a higher risk.
- Drugs used to treat cancer patients that contribute to the risk of venous thromboembolism include cisplatin, thalidomide, vinca alkaloids, fluorouracil, tamoxifen, bevacizumab, erithropoietin.
- Patients with a recent episode of VTE have a higher probability to be diagnosed with cancer within the first 6 months from such episode.

Primary prophylaxis

Based on the epidemiological data reported above, it has been hypothesized that primary antithrombotic prophylaxis is warranted in most ambulatory cancer patients (the issue of prophylaxis in hospitalized patients and in patients undergoing surgery will not be discussed). However, the presence of cancer is also associated with an increased bleeding risk (11). Furthermore, these patients are often treated with agents that contribute to the bleeding risk (e.g. drugs that reduce platelet count); finally, they may require diagnostic and therapeutic invasive procedures. The issue has been addressed by a number of studies, usually comparing a low molecular weight heparin to placebo. Among the most recent studies, PROTECHT (12) and SAVE-ONCO (13) showed a statistically significant reduction of VTE (HR 0.51 and 0.36 in patients treated with dalterparin, and semuloparin, respectively). Increased risk of bleeding and relatively low rates of clinically relevant events have reduced the impact of such observations. Costs and individual patients' acceptance of daily subcutaneous injections are also elements that must be taken into account when assessing the need for prophylaxis. Attempts have been made to develop risk scores in order to recognize those patients most likely to benefit from thromboprophylaxis. Khorana et al. have developed what is currently the most widely recognized score. The score assigns 2 points to very high risk cancers (pancreas and stomach), 1 point to high risk cancers (lung, lymphoma, gynecologic, bladder, testicular) and 1 point each to increased platelet count (≥ 350000/mm^3), anemia (hemoglobin < 10 g/dL) or use of red cell growth factors, increased leukocyte count (> 11,000/mm^3) and body mass index ≥ 35 (4). Other biomarkers currently under investigation include circulating tissue factor (TF), P-selectin, microparticles, factor VIII, prothrombin fragment F1+2, D-dimer (14). While it is likely that this approach will allow physicians to tailor thromboprophylaxis to the individual cancer patient based on the individual risk, most scientific societies currently do not recommend routine prophylaxis in ambulatory cancer patients. The lack of a general agreement is evident when recommendations from individual societies are analyzed. The American College of Chest Physicians suggests prophylaxis for patients with adjunctive risk factors and recommends against it in the absence of such factors, irrespective of the type and site of cancer (15). In contrast, the American Society of Clinical Oncology recommends to "consider" prophylaxis in all patients on an individual basis independent of type and site, and of the pres-

Most scientific societies currently do not recommend routine prophylaxis for VTE in ambulatory cancer patients.

ence or absence of risk factors (16). Finally, the National Comprehensive Cancer Network recommends to "consider" prophylaxis only in patients with high risk tumors and to avoid prophylaxis in all other patients, regardless of the presence of adjunctive risk factors (17). Clearly, more research is needed in order to take into account all the recently developed epidemiological data and the new candidate biomarkers described above.

Screening for occult cancer after an episode of VTE

Due to the high incidence of VTE in cancer patients, the probability of being diagnosed with cancer increases after an episode of VTE. Using population-based health registries available in Denmark, Sorensen et al. have analyzed data regarding over 77,000 patients with a diagnosis of VTE. The standardized incidence ratio for a diagnosis of cancer was approximately 5 for pulmonary embolism and 4 for deep vein thrombosis in the first six months after the episode of VTE. The figure dropped to 1.5 (for both deep vein thrombosis and pulmonary embolism) between six months and one year. After one year, the standardized incidence ratio was barely above one, and at most time points did not reach statistical significance. Of interest, patients with isolated superficial vein thrombosis showed similar standardized risks than VTE patients (18). Based on these, and other similar observations, the hypothesis that patients with VTE should be screened for incident cancer has been tested. A multicenter European study (19) assigned patients with a first episode of "unprovoked" VTE, i.e. an episode for which a predisposing factor such as trauma, surgery, acute disease, immobilization etc. is not immediately recognized, to a control group or to an "extensive screening" group. Patients in the extensive screening group underwent a complete set of diagnostic tests that included ultrasound and CT scanning of the abdomen-pelvis, gastroscopy or double contrast barium swallow, flexible sigmoidoscopy, serum tumor markers, haemoccult, sputum cytology, and gender specific tests (PSA, transabdominal ultrasound of the prostate, mammography, gynecological examination, PAP smear). Patients in the control group were managed by their primary care physicians per usual. Of interest, the study was hampered by difficulties with some local ethics committees that found it inappropriate to test only the patients in the experimental group, in the assumption that extensive screening would be beneficial even if costly. Even if underpowered for the reasons described, the study showed a significant decrease in the time to first diagnosis in the few patients that were eventually diagnosed with cancer; however, in most cases, the disease was diagnosed at similar stages compared to patients in the control group so that the delayed diagnosis in the latter likely had little or no impact on survival. To overcome the limitations of the study, the same Authors carried out a similar study a few years later to increase statistical power (20). When combined, the data from the two studies show a trend toward a reduction in cancer related mortality in the extensive screening group (HR 0.49; 95% CI 0.15-1.67) (21). The difference did not reach statistical significance; furthermore, the number of cancer related deaths was very small (8/199 in the control group and 4/197 in the screening group); these data, together with the physical and emotional discomfort for the patients related to the very demanding screening program, and with the cost of the program, suggest that extensive screening for cancer is not routinely warranted in patients with VTE. An approach based on individual characteristics that emerge after the initial history, physical examination, routine blood tests, and chest X-ray is for example what we recommend in patients admitted to our ward (22).

Controlled studies evaluating the benefit of extensive screening for occult cancer after an episode of VTE failed to improve survival.

The pathogenesis of thrombosis in cancer

The basis of cancer associated thrombosis are extremely complex and only partially understood. Although a thorough analysis of this topic is clearly beyond the scope of this review, we will describe some of the known mechanisms potentially relevant to the clinical issues described above. TF is an integral membrane protein expressed by tissues underneath the vessel wall; it is, therefore, extrinsic to blood. TF is an essential cofactor for coagulation factor (F) VIIa in the initiation of the so called extrinsic pathway of blood coagulation (Figure 1). The integrity of the endothelial vessel wall prevents the contact between TF and FVIIa so that the process of blood coagulation is activated only when the vessel wall is damaged (23). However, it has become clear over the last decades that TF can also be expressed by cells normally in contact with blood, including endothelial cells and leukocytes. The proinflammatory mediator tumor necrosis factor-alpha (24) and the platelet and endothelial cell associated adhesion molecule, P-selectin (25) are among the agonists known to induce TF synthesis in vascular cells. Thus, it would appear that a chronic "inflammatory" reaction mounted by the host as a non specific response to cancer contributes to the pathogenesis of VTE, similar to what happens for short periods of time during acute inflammatory and/or infectious diseases. These observations lend mechanistic support to the clinical observation described above that increased leukocyte count and soluble P-selectin are associated with an increased risk of VTE and represent potentially relevant biomarkers. How-

Cancer enhances proinflammatory mediators (e.g. TNFα and P-selectin) which activate the synthesis of procoagulant factors (e.g. tissue factor) with proangiogenic properties, thus favoring thrombosis.

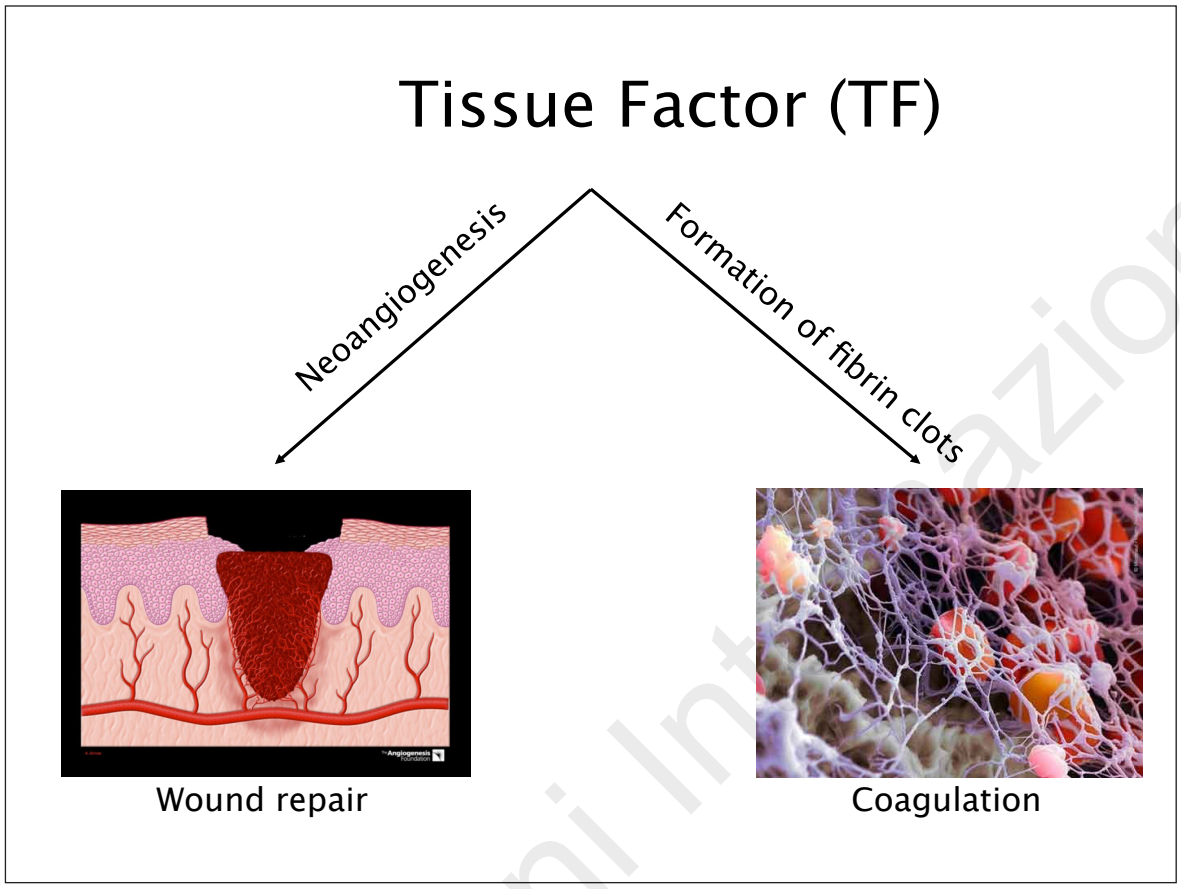

Figure 1 - Physiologic actions of tissue factor (TF).

ever, cancer cells themselves can express functionally active TF, directly contributing to the development of venous thrombosis. Cancers are considered "darwinian systems" exposed to selective pressures for autonomous proliferation and ultimately survival in the host. Due to their genetic instability, cancer cells have a very high rate of mutations and those that acquire favorable characteristics are more likely to survive (26). Thus, the question arises what advantage might be represented by TF expression by cancer cells. Seminal studies carried out over 20 years ago have shown that besides its role in the initiation of blood coagulation, TF has also a proangiogenic activity (27). It is not surprising that evolution has put the same molecule at the crossroad between two strictly related processes, i.e. blood coagulation and wound repair. Considering the well known importance of newly formed blood vessels for cancer growth, the evolutionary advantage represented by the synthesis of TF can be clearly recognized. These data contribute to explain the role of circulating TF, often associated with cell derived microparticles (28), as a biomarker for VTE risk.

Therapy

The standard therapeutic approach in VTE is based on an initial course of heparin or fondaparinux followed by vitamin K antagonists. The optimal duration of therapy is not established in all patients. While three months of vitamin K antagonists are usually recommended over shorter therapies, extended durations are considered when it is deemed that the risk of late recurrence exceeds the risk of bleeding events. This is usually the case after a second episode of VTE and might be the case after a first "unprovoked" episode of pulmonary embolism when the patient does not have a high bleeding risk (15).

Cancer patients might require different therapeutic strategies. As discussed, patients with cancer have increased risk of both recurrent thrombosis and bleeding. Furthermore, drug interactions and eating disorders (vomiting, hyporexia) make vitamin K antagonists titration particularly difficult; finally, the need for frequent invasive procedures that require discontinuation of oral therapy potentially contribute to the reduced performance of this therapy. Based on these considerations, the CLOT study compared a six month course of vitamin K antagonists (INR range 2-3) with the low molecular weight heparin, dalteparin (therapeutic, weight-

The first choice treatment for VTE in cancer patients remains low molecular weight heparin, but the new direct oral anticoagulants are currently being studied.

adjusted dose for the first 4 weeks followed by a reduction to approximately 75% of the initial dose for the following 5 months). The study showed a significant reduction in VTE recurrence in the dalteparin group during the 6-month study period (HR 0.48; 95% CI 0.30-0.77). There were no statistically significant differences in bleeding complications although the only fatal event was a massive hemoptysis in a patient with lung cancer treated with heparin (29). Of interest, a post-hoc analysis of the same data showed that in the subgroup of patients with limited disease dalteparin was associated with increased survival compared to vitamin K antagonists (30). The hypothesis that low molecular weight heparin might offer a survival advantage in patients with cancer has prompted numerous studies that have yielded as yet inconclusive results, although a meta-analysis suggests that patients with limited disease benefit from this therapy (31). *In vitro* studies have shown that low molecular weigh heparin exerts antiproliferative effects through the modulation of the cell cycle in cancer cells (32) thus supporting the hypothesis that these molecules have pharmacological effects that go beyond their direct antithrombotic properties. Despite these potentially interesting observations the use of low molecular weight heparin as an anticancer drug in patients without VTE is not recommended, even though the level of evidence is considered low to moderate (16). Current guidelines recommend a 6-month course of low molecular weight heparin at the dosage used in the CLOT study over vitamin K antagonists in cancer patients with VTE (15). Considering the well known risk of recurrent VTE in patients with active cancer, extended therapy is often preferable in such patients. No studies have formally addressed the issue whether low molecular weight heparin can be safely continued beyond the 6-month period analyzed in the CLOT study. Cost, need for extended chemotherapy, eating or absorption disorders and patients' preferences in terms of daily injections versus regular blood tests must be taken into consideration when deciding whether to switch from low molecular weight heparin to vitamin K antagonists after 6 months.

A new class of anticoagulants has been recently developed. The class comprises orally administered, direct inhibitors of either FIIa (dabigatran) or FXa (rivaroxaban and apixaban); a third direct FXa inhibitor, edoxaban, will likely be available in the near future. These molecules have the advantage of a predictable bioavailability and do not require monitoring. Drug interactions are also very limited compared to vitamin K antagonists. Data from the registration studies indicate that, as a class, these molecules are at least as effective as vitamin K antagonists in VTE and significantly safer, with some differences for individual molecules (33). Thus, it is expected that these so called direct oral anticoagulants (DOAC) will progressively replace vitamin K antagonists in the therapy of VTE. However, only few (approximately 4-5%) patients with active cancer were enrolled in the registration studies and therefore the data cannot be directly extended to this special population. A recent meta-analysis pooled data from a total of 1132 patients with cancer treated with a DOAC. No statistically significant differences were found in terms of recurrent VTE and bleeding events between patients treated with a DOAC and patients receiving conventional therapy (34). Of note, the data provide information about the comparison between DOAC and vitamin K antagonists, while the first choice treatment in cancer patients remains low molecular weight heparin. Furthermore, patients enrolled in these trials tended to have less severe forms of cancer and were less likely to be on active chemotherapy then, for example, the patients enrolled in the CLOT study. To date, DOAC are not registered for patients with active cancer. However, given the previously discussed lack of data for extended anticoagulant therapy beyond the 6-month period covered by the CLOT study even with low molecular weight heparin, DOAC are currently being used by some groups for extended therapy, at least in patients with less severe forms of cancer and presumably with no eating or absorption disorders. Both registry studies and ongoing controlled randomized clinical trials comparing DOAC with low molecular weight heparin are likely to provide in the near future much needed information about the best way to manage extended treatment in cancer patients after an episode of VTE. Table 2 summarizes the current principles of therapy in cancer-associated VTE.

Table 2 - Principles of therapy for cancer-associated VTE.

- Low molecular weight heparin is superior to vitamin K antagonists in patients with cancer in terms of prevention of recurring episodes.
- The standard therapy in patients with cancer consists of a 4-week course of low molecular weight heparin at full therapeutic dose, followed by 5 months at approximately 75-80% of the initial dose.
- In patients with active cancer undergoing chemotherapy, heparin is often preferred over vitamin K antagonists even after 6 months, but this approach is not supported by clear experimental data.
- The new direct oral anticoagulants have not been tested in cancer patients and are currently not indicated. New studies are underway to define their use in this population.

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