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MOLECULAR AND CLINICAL CONDITIONS ASSOCIATED WITH VENOUS THROMBOEMBOLISM IN ONCOLOGICAL PATIENTS

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The association between cancer and thrombophilia has been known since 1865 since Trousseau described it. However in the last three decades an increased interest has been raised on this issue related to several molecular and condition that are involved in the daily management of oncological patients. This brief review has been focused on molecular conditions underlying cancer acquired thrombophilia then to further clinical aspects inducing thrombophilia in oncological patients such as surgery, chemotherapy, concomitant medical illness and inherited thrombophilia.

Key Words: **cancer, thrombophilia, hypercoagulable state, inherited thrombophilia, chemotherapy.**

Venous thromboembolism (VTE) is a multifactorial disease, which may appear as deep venous thrombosis (DVT) of lower or upper limb, abdominal deep venous thrombosis and/or pulmonary embolism (PE). Of course, PE represent the most dangerous clinical manifestation and it may be classified as non-massive PE or massive PE that may lead to severe impairment of gas exchange and pulmonary hypertension inducing right ventricular dysfunction and/or heart failure then to be fatal within the first 30 min of symptom onset [1].

However, VTE recognizes inherited and acquired risk factors and cancer is the most common acquired thrombotic risk factor since Trousseau described this clinical association for the first time in 1865. On the other hand oncological patients with concurrent VTE are more at risk according to the data reported by Sorensen at al. [2].

Furthermore, during the natural history of oncological disease other thrombotic risk factors may be involved, so inducing a strong increase of VTE risk for oncological patients. This short review is focused to the evaluation of the main thrombotic risk factors in oncological patients.

CANCER ASSOCIATED THROMBOPHILIA

Malignancy usually shows prothrombotic properties *per se* related to the release of various prothrombotic molecules such as tissue factor (TF) and/or cancer procoagulant (CP) from malignant cells [3].

CP is cysteine proteinase produced by different types of malignant cells that may directly activate clotting factor X without the involvement of clotting VII pathway [3].

Yet, cancer cells may also express and release TF their self so inducing an hyperactivation of clotting cascade via clotting factor VII pathway [3]. Moreover, TF can also be expressed by endothelial cells or monocytes/macrophages because the involvement of cytokine network related to tumor growth, in particular, interleukin-1β and tumor necrosis factor α [3]. Furthermore, also release of clotting factor X by malignant cells has been rarely described [4].

Other molecular alterations associated with tumor growth and progression may be related to the involvement of fibrinolytic system. A specific interaction between cancer cells and extracellular matrix has been described because an impairment of protease/antiprotease balance causing an increased injury of extracellular matrix [5]. This impairment may modify the ability of cancer cells to the expansion also in the extracellular matrix so increasing the power of malignant growth and metastasis [5].

The effect of described activities is a cancer acquired thrombophilia that may also be divided in subclinical thrombophilia (i. e. hypercoagulable state) and clinical thrombophilia in which we may recognise an ongoing thrombotic event (e. g. VTE) [6].

CANCER AND HYPERCOAGULABLE STATE

A subclinical hypercoagulable state has been already described in oncological patients by several authors in the literature. Several tests, in fact, may testify the acquired hypercoagulable state present in cancer such as increased levels of d-dimer, prothrombin fragment 1 + 2 and/or thrombin-antithrombin complexes [7]. Although, we previously reported the underlying molecular mechanisms responsible for cancer acquired thrombophilia, also other conditions have been described in the literature. Some report, in fact, described an acquired protein C resistance [8] and/or increased levels of fibrinogen [9]; on the other

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Abbreviations used: CMF – cyclophospamide-methotrexate-fluoruracil; CP – cancer procoagulant; CVC – central venous catheter; DVT – deep venous thrombosis; G-CSF – growth colony stimulating factors; PaC – port-a-cath; PE – pulmonary embolism; TF – tissue factor; VTE – venous thromboembolism.

hand also hypofibrinolysis due to impaired levels of plasminogen activator inhibitor type 1 and/or type 2 has been reported [10–11].

A clinical hypercoagulable state may be defined as the clinical thrombotic manifestation (e. g. VTE) triggered by cancer acquired thrombophilia. On this topic we usually may find a venous thromboembolism but also other clinical manifestation such as arterial thrombosis [12] or disseminated intravascular coagulation [13] may be detected. However, in the last years several studies have underlined the association between cancer and VTE in order to promote also further studies on thromboprophylaxis of VTE in oncological patients [14–15]. Moreover, on this topic we should underline that VTE may appear usually as DVT of lower limb with following PE, but also unusual site of venous thrombosis during malignancy was described, such as abdominal deep vein thrombosis and/or spontaneous upper limb DVT.

CLINICAL CONDITIONS ASSOCIATED WITH VTE IN ONCOLOGY

Type of cancer. Since Trousseau described for the first time the association between cancer and thrombosis, several authors associated particular type of cancer to thrombotic complication. On this field Levitan et al. [16] confirmed that such type of cancer is more at risk of VTE complications such as pancreatic cancer, ovarian cancer or cancer localised to central nervous system.

Yet, further study underlined also another interesting aspect of oncological disease such as the staging. Advanced stage of oncological malignancy have been more frequently associated with VTE [17] if compared to early stage of malignancy.

Oncological surgery. Surgical procedures are the most common known risk factor for VTE. The association between major surgery and VTE, in fact, has been underlined by long time. Yet, surgical approach is usually related to post-surgical bed rest so adding another thrombotic risk factor. However, on this topic authors described a more common association between oncological surgery and VTE if compared to non-oncological surgery, although double blind randomised trial on these issues are lacking. Of course, benefits of thromboprophylaxis to prevent VTE for surgical management are clear for both oncological and non-oncological major surgery and have been demonstrated by several studies available in the literature [18–22].

Chemotherapy and other treatments. VTE has been already underlined in patients ongoing chemotherapy. First studies are available in the literature since 1980 and are focused mainly on patients affected by breast cancer in particular in advanced stage of disease [23–24]. In the following years several other studies focused the role of chemotherapy as additional risk factor for VTE in particular during treatment of haematological malignancies.

Furthermore, also specific drugs have been frequently involved in pathophysiology of acquired thrombophilia during chemotherapy. A common experience has been given by chemotherapy for breast cancer based on CMF regimen. CMF, but also other chemotherapeutical regimen, showed to reduce the levels of natural anticoagulant such as protein C and protein S in particular if associated with administration of tamoxifen [25]. Tamoxifen and other hormonal drugs, in fact, associated with chemotherapy, have been reported by several studies in the literature as thrombotic risk factors [25].

On the other hand, also growth colony stimulating factors (G-CSF) to fight chemotherapy-induced neutropenia showed a prothrombotic action [26].

Yet, in the last 10 years also thalidomide has been frequently associated with thrombotic complication during chemotherapy, while pathophysiological mechanisms involved are still the matter of discussion [27].

Central venous catheters and thrombosis. Central venous catheterisation is actually well established procedure in patients affected by malignancy in order to simplify delivery of several therapies such as chemotherapy, as blood transfusion and/or blood products administration, as parenteral nutrition, as fluids and other medication, in particular if peripheral venous accesses are lacking.

From this point of view we may distinguish central venous catheter (CVC) in central venous line (e. g. subclavian or jugular veins) or port-a-cath (PaC). However, since these procedures have been adopted an increased number of complications such as thrombosis and/or infections have been pointed out.

We may distinguish two several types of catheter-related thrombosis: a sleeve thrombosis on the outside of central venous catheter or a vascular thrombosis in which also the vein is involved by the thrombotic complication of CVC/PaC [28].

For this reason we observed also an increased incidence of upper limb DVT in the last decades if compared with previous data available in the literature in which this kind of venous thrombosis has been considered rare [29]. From a clinical point of view usually thrombotic complication of CVC/PaC are DVT of upper limb with frequent involvement of all the venous axis (e. g. extended venous thrombosis of axillar-subclavian and internal jugular axis) and this is a relevant data because subclavian and internal jugular DVT are frequently associated with PE.

Concomitant medical illness. Several patients affected by cancer may be affected by further medical illness that may lead to a further increase of risk of VTE. In these conditions we should include first of all recent immobility due to acute medical illness. Of course, immobility of oncological patients may be due to cancer disease *per se*, but frequently other conditions such as side effects of cancer therapies or following medical illness are present. Recent studies, in fact, underlined also medical illness, in particular if prolonged bed rest

is required, as additional risk factors for VTE in cancer patients such as severe infections, as heart failure, as chronic lung injury, as neurological disorders. The MEDENOX study [30], in fact, focused these clinical conditions alone or associated with oncological disease as relevant risk factor for VTE in patients admitted in hospital.

Inherited thrombophilia. A clear association between inherited thrombophilia and malignancy for oncological patients affected by VTE has not been investigated by large studies. However, several reports available in the literature showed that subjects carriers of inherited thrombophilia may not only show an increased incidence of thrombotic complications but also of relapse of VTE if affected by malignancy, if compared with subjects with malignancy and without thrombophilia. Yet, a preliminary report focused on upper limb DVT seems to underline a possible association between thrombophilia and malignancy [31]. On the other hand, a recent study based on a larger population did not confirm the association between inherited thrombophilia and VTE in patients affected by malignancy [32]. However, this study focused all venous thromboembolic events and not only upper limb DVT.

So, further studies are needed to understand the possible link and the effective role of inherited thrombophilia in oncological patients.

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МОЛЕКУЛЯРНЫЕ И КЛИНИЧЕСКИЕ ХАРАКТЕРИСТИКИ, АССОЦИИРОВАННЫЕ С ВЕНОЗНОЙ ТРОМБОЭМБОЛИЕЙ У ОНКОЛОГИЧЕСКИХ БОЛЬНЫХ

Связь между опухолевым процессом и гематогенной тромбофилией известна с 1865 г., когда Trousseau впервые дал ее описание. В последнее время отмечают возрастающий интерес к этой проблеме и связанным с ней молекулярным и клиническим параметрам, которые учитываются при постоянном наблюдении за больными онкологического профиля. Данный короткий обзор литературы посвящен характеристике молекулярных факторов, лежащих в основе тромбофилии, возникающей в процессе развития новообразований, а также другим особенностям клинического течения, индуцирующим тромбофилию у больных онкологического профиля, таким как хирургическое вмешательство, химиотерапия, сопутствующие осложнения и наследственная тромбофилия.

Ключевые слова: **рак, тромбофилия, гиперсвертываемость, наследственная тромбофилия, химиотерапия.**

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