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Coagulation Disorders in Pancreatic Cancer

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1. Introduction

The association between cancers and thrombosis is well known for a long period of time. In 1865 Armand Trousseau noted for the first time that unexpected or migratory thrombophlebitis could be a sign of an undiagnosed visceral malignancy (Trousseau, 1865). Some years later it is said that he observed this complication on himself in the context of an occult gastric cancer that caused his death (Khorana, 2003).

The risk of developing thrombosis in cancer patients is considered to be increased 2- 7 fold compared with persons without cancer (Bloom et al, 2005; Heit et al, 2004). This risk is dependent on many factors. According to the type of tumor, the risk is thought to be the highest in tumors of the ovary, pancreas and central nervous system. Also the extent of the tumor, the presence of metastasis, age, immobility and the type of therapy increase this risk. Surgery for cancers (Rahr & Sørensen, 1992) and chemotherapy (Levine, 1997) are both associated with an important risk of venous thrombosis and embolism. In a large case-control study that included 3220 patients with cancer, it was reported an overall 7 times increased risk for venous thrombosis that depend on type of cancer and time since the cancer diagnosis. A very high relative risk was found for gastrointestinal, lung and hematological malignancies. Advanced stage of disease was associated with a further increase in risk (Blom et al, 2005).

Patients with cancer who develop venous thromboembolism have a poor prognosis than those without this vascular complication. The risk of recurrent thromboembolism and death from any cause is greater than three fold in patients with cancer compared to those without malignancy (Levitan et al, 1999).

Epidemiological studies looking for the incidence of cancer in patients with thromboembolic events found out that in 15-20% of patients, thromboses were associated with malignancy (Er & Zacharsky, 2006).

The association of cancer and thrombosis raises two distinct problems. On one hand, the diagnosis of thrombosis in one patient may represent, in some situations, a sign of an occult malignancy. On the other hand, a patient with cancer may develop some time, in the evolution of his malignant disease, a thromboembolic event, which may worsen his

prognostic. That is why, for the clinical practice, the diagnosis of these associated diseases is very important.

2. Epidemiology of thrombosis in pancreatic cancer

Pancreatic cancer (PC) is known to be associated with a higher incidence of venous thromboembolism than other cancers. The first publication that noted the high incidence of thrombosis in PC was a postmortem study done in 1938 (Sproul, 1938). Since that, several other studies have been conducted and the incidence found ranges from 5% to 60% (Sack et al, 1977; Khorana & Fine, 2005).

In a cohort study of 202 patients with a first diagnosis of pancreas carcinoma the authors found that the risk of venous thrombosis is 6-fold increased compared with the general population, at a cumulative risk of 10% (Blom et al, 2006). In this study, tumors of the corpus and cauda of the pancreas had a 2-3-fold increase risk of venous thrombosis than tumors of the caput of the pancreas (Blom et al, 2006). Similar results showing a higher incidence of thrombotic events for tumors located in the corpus and cauda of the pancreas were reported by other authors (Sproul, 1938; Sack et al, 1977; Bick, 1992; Pinzon et al, 1986).

In a retrospective single institute study 6,870 patients with pancreatic cancer were evaluated for venous and arterial thrombosis. The incidence of all thrombotic events was 19% with venous thrombosis accounting for 17%, arterial thrombotic events for 2% and associated venous and arterial events in 0.9% of cases. Pulmonary embolism was found in 25% of patients with venous thrombosis (Epstein et al, 2010)

The risk of venous thrombosis increases in the presence of metastases. Blom and colab. found a 2-fold increase risk of venous thrombosis in patients with distant metastases, after adjusting for age, sex, surgery and chemo- or radiotherapy (Blom et al, 2006).

The risk of developing thrombosis is further increased with chemotherapy (Heit, 2002; Wall, 1989) and also with surgical treatment. Patients with PC treated with chemotherapy had a 4.8-fold increased risk of thrombosis compared to those without chemotherapy. The same study showed no significant increase in thrombotic risk patients treated with radiotherapy (Blom et al, 2006).

Patients with malignancies submitted to surgery have at least twice the risk of postoperative venous thrombosis and more than 3 times the risk of fatal PE compared with non-cancer patients undergoing a similar procedure (Geerts et al, 2004).

In patients with PC submitted to surgery there was a 4.5-fold increase in the risk of venous thrombosis during the postoperative period of 30 days (Blom et al, 2006).

The incidence of fatal pulmonary embolism was also evaluated. In one study 4 out of 541 (0.7%) died from pulmonary embolism (Neoptolemos et al, 2001). Concordant results were reported in another study that found 2 of 202 patients (1%) with fatal pulmonary embolism (Blom et al, 2006).

3. Pathogenesis of thrombosis in pancreatic cancer

The mechanisms underlying the association of venous thromboembolism with pancreatic cancer are not completely understood. Large and relevant data suggest an implication of

coagulation systems and increased angiogenesis. It is considered that activation of hemostasis in pancreatic cancer causes thrombosis but also tumor angiogenesis (Browder et al, 2000).

The key molecule in this process seems to be *tissue factor* (TF), the main physiologic initiator of the extrinsic pathway of coagulation (Gouaulthelmann & Josso, 1979; Nemerson, 1988). TF plays also an important role in angiogenesis (Mechtcheriakova et al, 1999; Zhang et al, 1994).

TF, also called platelet tissue factor, factor III, or CD142 is a protein present in subendothelial tissue, platelets, and leukocytes. TF consists of three domains: extracellular that binds factor VIIa, transmembrane and intracellular involved in the signaling function (Nemerson, 1988). In healthy individuals there are little circulating amounts of active TF. In response to specific stimuli such as inflammation, malignant processes, its expression increases (Ruf et al, 2000; Wada et al, 1995).

As an initiator of coagulation, TF binds and activates factor VIIa, resulting in TF-VIIa complex which activates factor X leading to the synthesis of thrombin essential in clot formation (Gilbert & Arena, 1995). The activity of TF is regulated by several factors. The most important is TF pathway inhibitor which is composed of three different domains: the first inhibits FVII, the second inhibits FX and the function of the last one is still unknown (Broze, 1995; Girard et al, 1989; Ehrlich et al, 2011). TF pathway inhibitor is secreted by endothelial cells.

The expression of TF can be controlled by epidermal growth factor receptor (Milsom et al, 2008) and by FX activated. Increased concentrations of FX activated inhibit the synthesis of TF (Ettelaie et al, 2007).

In cancers, TF is present on malignant cells and also on endothelial cells (Rickles et al, 2003). Some previous data indicate that TF is expressed in pancreatic malignant cells. It correlated with advanced histological stages and with a poor prognosis (Kakkar et al, 1995; Nitori et al, 2005). In a retrospective study, Khorana and colab. investigated the expression of TF in non invasive and invasive pancreatic cancers. They found an increased expression of TF in 77% of patients with pancreatic intraepithelial neoplasia and in 91% of patients with intraductal papillary mucinous neoplasms, two non invasive precursors of invasive pancreatic cancer. They concluded that TF expression is an early event in pancreatic cancer. In patients with pancreas resection, TF expression correlated with expression of vascular endothelial growth factor (VEGF) and increased neovascularization, suggesting an implication of TF in angiogenesis. They found an incidence of thromboembolism of 26.3% in patients with high TF expression levels compared to 4.5% in those with low expression of TF, suggesting an important role of TF in cancer associated thrombotic complications. (Khorana et al, 2007).

Angiogenesis has been documented in pancreatic cancer and it was associated with a rapid tumor growth and a poor prognosis (Lomberk, 2010).

The process of angiogenesis represents the formation of new blood vessels from the pre-existing vascular bed. In cancers angiogenesis contributes to tumor growth (Folkman, 1995).

Pancreatic cancer seems to be accompanied by an important increase in angiogenesis that is linked to the activation of coagulation. Proteins of coagulation are involved in angiogenesis

in two different ways, one clotting dependent and the other one clotting independent (Echrisch et al, 2011). The clotting dependent mechanism is initiated by the activation of TF receptors. TF activates then the coagulation cascade that leading to fibrin formation and platelet activation (Falanga & Rickles, 1999). Activated platelets release mediators that promote angiogenesis such as VEGF, beta fibroblast growth factor (β -FGF) and platelet growth factor (PGF) (Palumbo et al, 2000; Echrisch et al, 2011). In clotting independent mechanism thrombin plays a very important role by inducing the proteolytic cleavage of protease-activated receptors (PAR) (Traynelis & Trejo, 2007). The activation of PAR stimulates the synthesis of factors implicated in angiogenesis such as VEGF (Liu & Mueller, 2006).

Another mediator that involved in thrombosis and angiogenesis of pancreatic cancer is epithelial growth factor receptor (EGFR). An increased expression EGFR was noted in pancreatic cancer and correlated with enhanced angiogenesis, tumor growth and unfavorable evolution (Yamanaka et al, 1993).

Microparticles have also been studied in relation with thromboembolism in cancer. Microparticles are membrane vesicles released from stimulated or apoptotic cells in normal persons but they are also implicated in the activation of coagulation (Diamant et al, 2004).

Many recent data support the role of microparticles (MP) and of TF-MP complex in thrombotic complications of patients with malignancies (Tilley et al, 2008).

The level of TF activity associated with TF/MP seems to be higher in PC compared with other types of cancer. From the group of patients with cancer and thrombosis those with pancreatic malignancies have the highest TF activity (Tesselaar et al, 2009).

The role of *P-selectin* in thrombosis in these patients was also studied during the last two decades. P-selectin is released from platelets and endothelial cells and contributes to the adhesion of leucocytes on activated platelets and thrombus formation and to adhesion of cancer cells to stimulated endothelial cells. Experimental studies that have been done on primates suggest that P-selectin inhibition is as effective as low molecular weight heparin in promoting thrombus resolution and in preventing re-occlusion (Chen & Geng, 2006). In humans elevated levels of P-selectin may be predictive of thromboembolism in patients with cancers (Ay et al, 2008).

A large case-control study of venous thrombosis in patients with cancer found that the presence of factor V Leiden or prothrombin 20210A mutation increases by 12 to 17-fold the risk of developing thrombosis compared to those with out these modifications (Blom et al, 2005).

Activation of endothelium by tumor-derived inflammatory cytokines, which could induce expression of various adhesive molecules such as V-CAM and E-selectin may promote the thrombotic process in cancer patients (Varki, 2007).

Thromboembolic events in PC patients are also influenced by particular conditions that generally increase the risk of thrombosis such as immobilization, advanced age, comorbidities (infections, cardiac or respiratory failure, obesity, etc.), history of venous thrombosis (Offord et al, 2004; Echrisch et al, 2011). Also, the local effects of a great tumour, such as venous compression, that can predispose to an increased risk of thromboembolism (Dumitrascu et al, 2010).

Central vein catheterization used for the administration of cancer therapy represents a risk factor for thrombosis in these patients. Patients with distant metastases have more increased risk for thrombosis in absence of antithrombotic prophylaxis. The incidence of clinically overt venous thrombosis in cancer patients with central venous catheter ranges from 0.3% to 28%, and rises to 27% - 66% when the diagnosis was assessed by venography (Verso & Agnelli, 2003; Verso et al, 2008).

Chemotherapy has been shown to be an independent risk factor for thrombosis in cancer patients. In a large population based study, the risk of thrombosis was increased 6.5 fold in patients receiving chemotherapy and 4,1 fold in patients with cancer not receiving this kind of therapy, compared to patients without malignancies (Heit et al, 2000, Kirwan et al, 2011). The risk is additionally increased if chemotherapy is combined with steroids (Shen et al, 2011) or erythropoietin (Bennet et al, 2008). The inhibitors of angiogenesis (thalidomide, lenalidomide, bevacizumab, sunitinib, sorafenib, and sirolimus) used as novel antineoplastic therapy are associated with an increase in arterial and venous thromboembolism and hemorrhage (Zangari et al, 2009). Gemcitabine is a deoxycytidine analogue related to cytarabine, that has been shown to improve evolution in patients with advanced PC. Deep venous thrombosis was found in one study in 3.2% of patients treated with gemcitabine (Kaye,1994).

4. Clinical outcome in pancreatic cancer patients with thrombosis

Patients with PC may present with signs of venous or arterial thrombosis. Venous thrombosis is more frequent and it can affect peripheral or visceral veins (Blom et al, 2006). Migratory superficial thrombophlebitis is highly suggestive for a malignancy (Fig. 1). Of the visceral vein thrombosis portal thrombosis has a very high incidence. In one study portal vein thrombosis was found in 32 of 108 patients (30%) and it was associated with a poor prognosis (Price et al, 2010). Perpancreatic veins may also be involved (Fig.2).

The diagnosis is suggested by clinical signs and is usually confirmed ultrasonographically (Fig. 3 and 4).

Disseminated intravascular coagulation is another coagulation disturbance described in PC. It was associated with an increase in circulating TF (Ueda, 2001). This complication was also observed in patients suffering from metastatic pancreatic cancer treated with a recombinant adenoviral vector containing the cloned human wild type p53 suppressor gene (Haag, 2000).

It is generally reported that patients with cancer and thrombotic complications have a poor prognosis (Levitan et al, 1999; Sorensen et al, 2000). In the retrospective study by Epstein and colab., 24% of patients with PC and thromboembolism, experienced pulmonary embolism. The authors found a reduced overall survival for patients with a thromboembolic event (12.9 month) if compared to those without (13.4 month). Treatment consisted of low molecular weight heparin, in 95% of patients and inferior vena cava filter was necessary in 19%. Patients with occult thrombotic events or with thrombosis diagnosed at the time of cancer diagnosis, had a poorer survival (6.2 month) compared with those with secondary thrombotic events (13.7 month) (Epstein et al, 2010; Shah& Saif, 2010).

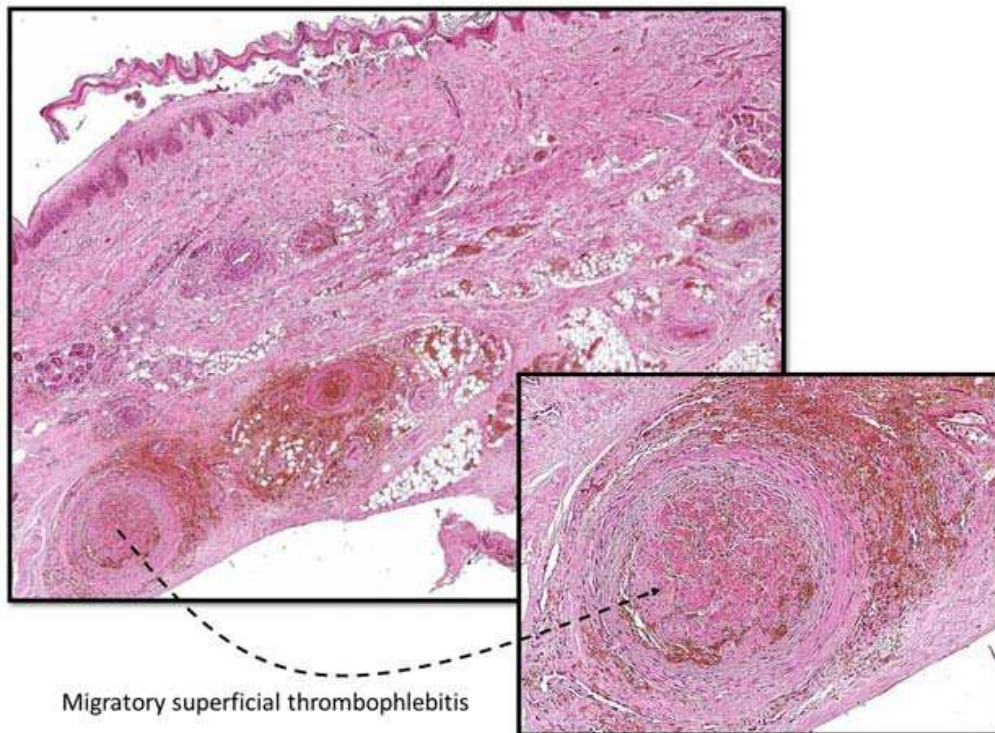


Fig. 1. Migratory superficial thrombophlebitis in a case of PC (hematoxylin-eosin staining of superficial veins)

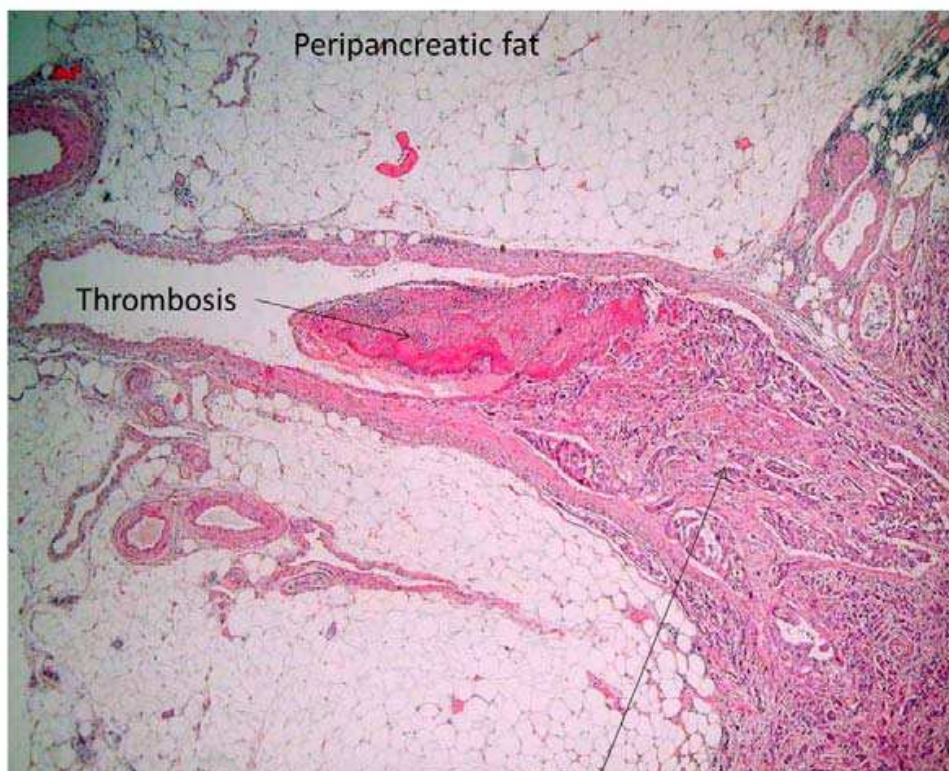


Fig. 2. Vascular invasion of PC with local vein thrombosis (hematoxylin-eosin staining)

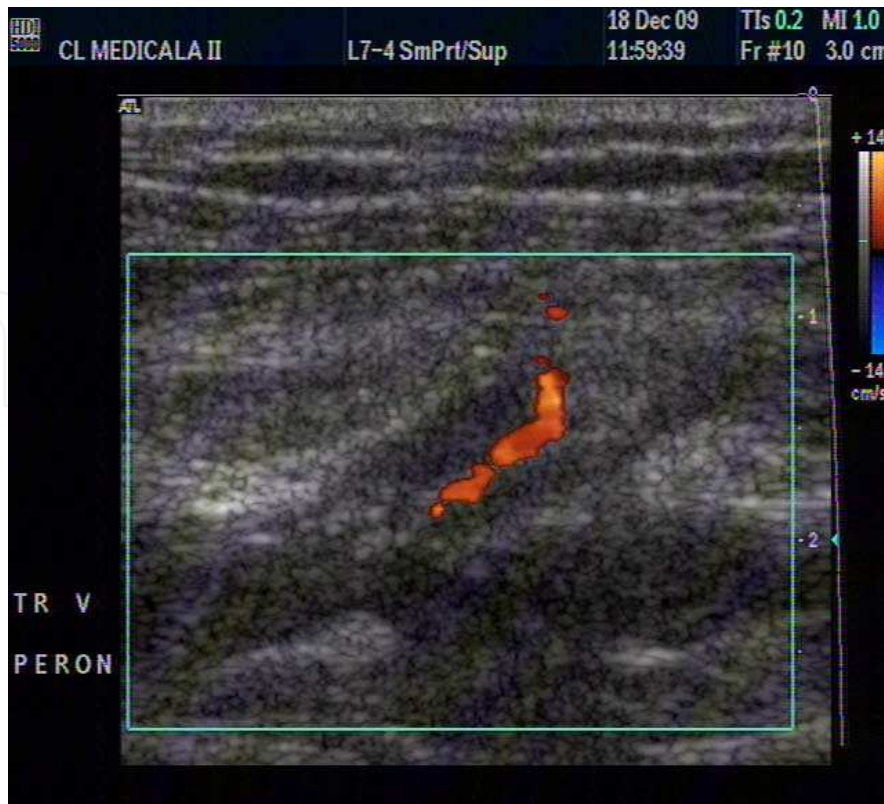


Fig. 3. Thrombosis of peroneal vein in a patient with PC (2D and colour Doppler echographic examination)



Fig. 4. Thrombosis of femoral vein in a patient with PC (2D echographic examination)

Looking for possible predictors of thromboembolism in pancreatic cancer, one previous study showed that higher levels of TF expression in tumor cells were associated with nearly 4 fold increase in venous thrombosis (Khorana et al, 2007). In a recent retrospective study that included patients diagnosed with pancreaticobiliary cancers between January 2005 and December 2008, looked for the association of TF with thromboembolism and survival. This study included 117 patients with a median age of 65 years of which 68% had pancreatic cancer and 29% biliary cancers. Thrombotic complications were found in 52 (44.4%) patients. Elevated levels of TF (greater than 2.5pg/ml) were associated with thromboembolic events (odds ratio=1.22;p=0.04). Also, TF levels were predictive for a worse overall survival (hazard ratio=1.05; p=0.01) (Barthuar et al, 2010). These results if confirmed in prospective studies suggest that TF expressed by neoplastic cells or plasma levels of TF could be used as independent predictive biomarkers for thromboembolic events in PC patients and also in other cancers (Khorana et al,2007; Barthuar et al, 2010).

5. Prevention and treatment of thromboembolism in PC

5.1 Prophylaxis of venous thrombosis

Epidemiologic and pathogenic data clearly indicate that patients with malignancy had an important risk of thromboembolic events. In practice, risk stratification can be used to classify patients according to their thrombotic risk. The ACCP guidelines consider the patient with cancer in the very high risk category particularly when surgery is recommended. Other factors that may increase patient's risk are age, immobilization, prior history of venous thrombosis, obesity and central venous catheter (Geerts et al, 2004; Caprini et al, 2001).

Prophylaxis in cancer is indicated mainly in two distinct situations: in patients undergoing surgery and in medical patients receiving chemotherapy.

Patients undergoing abdominal surgery are a particularly high-risk population who may benefit for extended thromboprophylaxis. Low molecular weight heparins are preferred as they showed to be as effective and safe as unfractionated heparin. Several studies showed a reduction in thromboembolic complications in patients receiving prolonged prophylaxis for 3 or 4 weeks compared to those with 1 week of treatment in postoperative period. This beneficial effect was not accompanied by an increase in hemorrhagic complications (Bergqvist et al, 2002; Rasmussen et al, 2003).

In patients treated with chemotherapy antithrombotic prophylaxis showed also a reduction in thromboembolic risk. There are 2 trials in patients with PC treated with gemcitabine and a low molecular weight heparin and another one in which a low molecular weight heparin was associated to a combined chemotherapy gemcitabine and cisplatinum.

The results of the Charité Onkologie (CONKO)-004 trial were recently published. The principal objective of this trial was the evaluation of the reduction in symptomatic thromboembolic events in patients with advanced PC. The second end point was the overall survival. Between April 2004 and January 2009, 312 patients with histological confirmed advanced PC were randomized into two groups as follows: 160 patients received treatment with enoxaparin 1 mg/kg once a day for 3 months, followed by 40 mg daily and 152 did not receive antithrombotic prophylaxis. The results indicated a significant reduction of

symptomatic thromboembolism in treated patients after 3 month (1.25% compared to 9.87% in non treated patients). This significant difference was also found after 12 months with an incidence of 5% in treated patients compared to 15.13% in non treated arm of the trial. There were no significant major hemorrhagic complications in both groups. The median overall survival was not different between the two groups (9.92 month in treated patients versus 8.15 month in no treatment group; $p=0.054$), for a median follow up period of 45.44 months (Reiss et al, 2010).

In the FRAGEM (Chemotherapy With or Without Dalteparin) trial, 123 patients were randomised to receive dalteparin. This study showed also a significant reduction in thromboembolic events in patients receiving prophylaxis (Maraveyas et al, 2007).

The third trial aimed to assess the effects of the addition of low molecular weight heparin (nadoparin) to gemcitabine plus cisplatin combination in 42 patients with advanced PC. The results showed a better mean time to progression in the group receiving prophylaxis (6.0+/-0.9 months) when compared to control group (3.0+/-1.5 months) ($p=0.0001$). Also median overall survival time for the nadoparin group was 9.0+/-1.9 months compared to 4.0+/-0.4 months ($p=0.0034$) in the control group (Icli et al, 2007).

The results of these trials showed that the association of a low molecular weight heparin to chemotherapy in advanced pancreatic cancer patients reduces the risk of thromboembolic events. However, the CONKO-004 did not found any improvement in the overall survival and time to progression. This needs to be verified in future prospective trials.

In patients with central vein catheter used commonly for the administration of chemotherapeutic agents and parenteral nutrition, anticoagulation is not recommended for routine prophylaxis of catheter related thrombosis in cancer patients (Geerts et al, 2004). Even if early studies showed risk of venous thrombosis related to central vein catheters (Montreal et al, 1996), a large multinational trial that investigated the efficacy of dalteparin in preventing catheter related thrombosis, found that the risk of thrombosis was not significantly different in the group treated with dalteparin compared to placebo-treated patients (Karthaus et al, 2006). Prophylaxis in patients with central vein catheters may be imposed sometimes when additional risk factors are detected.

5.2 Treatment of venous thrombosis

Treatment of venous thrombotic complications in patients with cancer is usually difficult due to the risk of recurrences and at the same time of bleeding with severe consequences. The aims of treatment are reduction of clinical manifestations of thrombosis and of the risks pulmonary embolism and postthrombotic syndrome.

The treatment of choice is the administration of a low molecular weight heparin for one week followed by an oral anticoagulant (vitamin K antagonist). Low molecular weight heparins have been shown to be as effective and save as unfractionated heparin. They are preferred like first line treatment because usually no laboratory monitoring is necessary, and the risks of developing heparin induced thrombocytopenia and osteoporosis is reduced. Also the administration of this type of heparin is convenient using once or twice daily doses as subcutaneous injection (Dolovich et al, 2000; van den Belt et al, 2000, Er & Zacharski, 2006).

Recurrent thrombosis needs long-term management. In cancer patients prolonged anti thrombotic, particularly with oral antivitamin K medication, is associated with increased risk of hemorrhagic complications that may be linked to malnutrition, liver dysfunction and metastases, reduced alimentary intake or vomiting. The risk of bleeding appears to correlate with the extent of the disease. In a study that investigated the risk of bleeding in patients with different extent of the disease, patients with moderately extensive cancer had a 2-3-fold increase in risk of major bleeding; patients with extensive cancer had a 5-fold increase in this risk (Prandoni et al, 2002).

Low molecular weight heparins are now preferred as long term secondary prevention treatment in these patients. This indication is based on the results of several randomized trials that showed a superior efficacy and safety of low molecular weight heparins compared with oral anticoagulants in long term administration. In a multicenter randomized trial patients were treated for 3 month with enoxaparin or with warfarin. Of the group receiving warfarin 15 (21%) of 71 patients had a major bleeding or a thrombotic recurrence, compared to 7 (10.5%) of 67 patients treated with enoxaparin (Meyer et al, 2002). A large multicenter trial, „The Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) compared treatment with dalteparin with oral anticoagulant therapy. After 6 months of treatment the probability of recurrent venous thrombosis was 17% in patients receiving oral anticoagulation compared to 9% in those treated with dalteparin. There were no significant differences between groups for the hemorrhagic complications (Lee et al, 2003).

5.3 Antineoplastic effects of anticoagulants

There are evidences that anticoagulant therapy may have also anticancer effects. Heparins in addition to activation of antithrombin, may promote the release of the tissue factor pathway inhibitor from the endothelium that blocks tissue factor expressed by tumor cells (Alban, 2001; Sandset et al, 2001). Heparin is also able to bind to and to inhibit some inflammatory cytokines that can activate endothelial cells and increase expression of adhesion molecules (Elsayed & Becker, 2003; Varki ,2007). Heparin may interfere with formation of the platelet "cloak" around tumor cells suggesting a possible effect in metastasis prevention (Borsig et al, 2001).

Several clinical studies support the efficacy of heparins in improving tumor response and survival. The administration of nadroparin in patients with advanced solid cancers increased median survival to 8 month compared to 6.6 months in patients receiving placebo, after 6 weeks of treatment (Klerk et al, 2005). Dalteparin associated in the treatemnt of patients with small cell lung cancer, for 18 weeks improved tumor response and median overall survival from 8 to 13 months (Altinbas et al, 2004).

Beneficial effects have also been reported for warfarin in cancer patients. A prospective randomized trial showed that survival of patients with small-cell lung carcinoma had a significant prolonged survival if warfarin was added to standard therapy. The median survival and the time to first evidence of disease progression were increased in patients receiving warfarin (Zacharski et al, 1981).

Data suggesting the participation of coagulation mechanisms in tumour growth are important arguments for researchers to explore this novel therapeutic strategy in cancer patients.

6. Conclusions

Pancreatic cancer is associated with a very increased risk of thromboembolic events. The mechanisms underlying this association are complex and multifactorial but are not yet clearly understood. Thromboembolic complications in patients with PC indicate a poor prognosis and a reduction of life expectancy. Antithrombotic prophylaxis in advanced PC treated with chemotherapy reduces the risk of embolic complications and it may also improve survival and time to progression of cancer in these patients. The medication of choice in preventing and treating thrombosis are low molecular weight heparins. Anticoagulant therapy may help cancer patients due also to a possible antitumor effect.

7. Acknowledgements

This work was partly funded by the research grant INFORAD of the Romanian Ministry of Education and Research.

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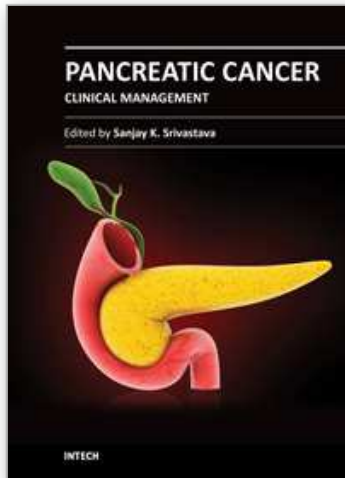
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Pancreatic Cancer - Clinical Management

Edited by Prof. Sanjay Srivastava

ISBN 978-953-51-0394-3

Hard cover, 312 pages

Publisher InTech

Published online 28, March, 2012

Published in print edition March, 2012

This book covers pancreatic cancer risk factors, treatment and clinical procedures. It provides an outline of pancreatic cancer genetic risk factors, biomarkers and systems biology for the better understanding of disease. As pancreatic cancer suffers from lack of early diagnosis or prognosis markers, this book encompasses stem cell and genetic markers to identify the disease in early stages. The book uncovers the rationale and effectiveness of monotherapy and combination therapy in combating the devastating disease. As immunotherapy is emerging as an attractive approach to cease pancreatic cancer progression, the present book covers various aspects of immunotherapy including innate, adaptive, active, passive and bacterial approaches. Management of anesthesia during surgery and pain after surgery has been discussed. Book also takes the reader through the role of endoscopy and fine needle guided biopsies in diagnosing and observing the disease progression.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

A. Albu, D. Gheban, C. Grad and D.L. Dumitrascu (2012). Coagulation Disorders in Pancreatic Cancer, Pancreatic Cancer - Clinical Management, Prof. Sanjay Srivastava (Ed.), ISBN: 978-953-51-0394-3, InTech, Available from: <http://www.intechopen.com/books/pancreatic-cancer-clinical-management/coagulation-disorders-in-pancreatic-cancer>

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