Women with Thrombosis and Cancer

WHITH 2015: ASPEN/ITAC-CME LUNCH SYMPOSIUM
February 14, 2015

The purpose of this communication is to provide a summary, key messages, discussions, and feedback of the Thrombosis and Cancer in Women Lunch Symposium, presented by the International Initiative on Thrombosis and Cancer (ITAC)-CME, which was held on February 14th, 2015 at the 6th International Symposium on Women’s Health Issues in Thrombosis and Haemostasis (WHITH), in Berlin, Germany.

This symposium marks the beginning of an accredited educational continuum by the Women, Thrombosis, and Cancer (WTC) initiative, designed to gather data and clinical insights globally, including clinical care gaps in the diagnosis, management, and monitoring of women with cancer at risk of thrombosis.

This symposium was accredited as a single event by the European Council for Continuing Medical Education (EACCME) for up to 2 hours of European external CME credits. The EACCME is an institution of the European Union of Medical Specialists (UEMS), www.uems.net.

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LEARNING OBJECTIVES

At the end of the presentation, participants will be able to:

1. Review diagnostic and treatment duration considerations of venous thromboembolism in myeloproliferative disorders
2. Identify the risks and consequences of thrombosis and cancer in special female populations
3. Assess factors associated with central venous catheters that may influence the occurrence of venous thromboembolism and its management in breast cancer
4. Discuss the clinical utility of a mobile app for implementing the international guidelines, including pro and con perspectives
CLINICAL GAPS

ITAC-CME has completed a thorough analysis of educational needs and practice gaps in clinical care in order to tailor educational programs accordingly. Through an evaluation of peer-reviewed literature and clinical trials, interviews with thought leaders about educational opportunities, and surveys among potential participants regarding topics of interest and challenges to changing practice behaviours, ITAC has identified gaps in knowledge and practice behaviours related to the prophylaxis and management of venous thromboembolism (VTE) events that affect patients with cancer.

These gaps were validated at this symposium through interactive polling questions, whereby many differences in care were seen among participants related to specific management decisions in women with cancer, indicating a lack of consensus and a knowledge gap, as seen below:

- The increasing prevalence of VTE in cancer patients, including central venous catheter-related thrombosis, underscores the urgent need to optimize clinical practice. An accredited educational continuum developed by the WTC initiative will help to close these gaps and ultimately optimize clinical practice and improve the outcomes of women with cancer and thrombosis.

**This WTC initiative was made possible through an unrestricted educational grant from Aspen Pharmacare.**
OVERVIEW
(Dominique Farge-Bancel, France)

The burden of cancer, which is a leading cause of death, is increasing as a result of a growing aging population, which is a particular concern for women as they tend to live longer. Worldwide, there are 17.2 million women living with cancer in 2012, with 6.7 million new cancer cases and 3.6 million cancer deaths.

Breast cancer is the most frequent cancer among women worldwide and the second cause of cancer death followed by lung and colorectal cancers. Gynecologic cancers are also common in women around the world, including cervical, uterine, and ovarian cancers. Women’s cancers potentially have a greater burden on society than men, as women are the main providers for their children’s health and education; they often manage their partner’s health needs; and many women take care of an aging or chronically ill relative. Women also comprise a significant proportion of the workforce in many countries and are taking on high-profile leadership roles in government and business worldwide. With an increase in female participation in social, educational, economic, and political spheres, addressing women’s health is a necessary and effective approach to strengthening health systems overall.

Unfortunately, few clinicians appear to be aware of the higher risk of thrombosis in cancer patients. VTE, including deep-vein thrombosis (DVT), pulmonary embolism (PE), or central venous catheter-related thrombosis (CRT), is the second leading cause of death in cancer patients.
Physicians underestimate the increasing prevalence of VTE in patients with cancer; 50% of deceased cancer patients are found to have a VTE on autopsy, but only 4 to 20% of patients with cancer are diagnosed with a VTE. In addition to the thrombotic risk associated with cancer itself (via procoagulant activities and cytokine release by tumour cells, as seen on the right), chemotherapy is also strongly associated with VTE. Cancer alone is associated with a 4.1-fold risk of thrombosis, whereas chemotherapy increases the risk 6.5-fold. Furthermore, there are various factors that can increase the risk of VTE among cancer patients, including patient-related factors, such as age and comorbidities, cancer-related factors, such as the type of cancer and advanced disease, and treatment-related factors, such as recent surgery, chemotherapy, hospitalization, and use of central venous catheters. Moreover, pregnancy and use of hormone therapies can also increase the risk of VTE, which is particularly concerning for women.

Prevention and treatment of VTE in women with cancer are essential to patient survival. Unfortunately, few clinicians appear to be aware of the higher risk of thrombosis in cancer patients, and with the steady increase of female participation in social, educational, economic, and political spheres, addressing women’s health is a necessary and effective approach to strengthening our social fabric and health systems overall.

Myeloproliferative Disorders in Women
(Martin Ellis, Israel)

The myeloproliferative neoplasms (MPNs) are a group of diseases that are unique in regard to their molecular characterization. In the World Health Organization classification of Hematologic malignancies, this group of diseases includes chronic myeloid leukemia (CML), which is Philadelphia chromosome-positive, as well as three diseases which are Philadelphia chromosome-negative, including essential thrombocythaemia (ET), polycythaemia vera (PV), and idiopathic myelofibrosis (MF). Most Philadelphia chromosome-negative MPNs have a unique acquired point mutation in the JAK2 gene (JAK2 V617F), found in > 95% of PV cases and 60% of ET and MF cases. Mutations in the calreticulin protein (CALR) have also been found in the majority of JAK2 and MPL-negative patients, found in 20 to 30% of ET and MF cases.
MPNs are associated with an increased risk of thromboembolic events and represent an important cause of death in these diseases. PV patients in particular are at a higher risk of thrombosis, with a 20 to 30% incidence of VTE. The JAK2 mutation has been found to increase thrombosis in mice, which is most strongly associated with PV patients. Interestingly, women with MPNs, particularly PV and MF, appear to be at a higher risk than men for thrombosis. In addition to an increased incidence of splanchnic vein thrombosis, women with PV also have an earlier age of onset, a higher platelet count, and more splenomegaly. Unfortunately, there is no consensus how PV patients with thrombosis should be treated. Women deserve particular attention in this topic going forward.

Thrombosis and Cancer in Special Female Populations

(Benjamin Brenner, Israel)

The risk of VTE can vary during the course of malignancy, underlining the need for frequent patient monitoring and individualized prophylaxis and treatment.

There are three overarching risk factors for VTE: hypercoagulability, venous stasis, and alteration of the vascular wall, known as the Virchow triad. Cancer links all three conditions of the Virchow triad and puts patients with cancer at increased risk of DVT, PE, and/or CRT.
The following shows the patient-, cancer-, and treatment-related factors that can influence or increase the risk of VTE in a patient with cancer.

<table>
<thead>
<tr>
<th>Risk Factors for VTE in Patients with Malignant Disease</th>
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<tbody>
<tr>
<td><strong>Patient-related factors</strong></td>
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<tr>
<td>• Older age (esp. &gt;65)</td>
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<tr>
<td>• Race (Black/Asian &gt; Hispanic/Caucasian)</td>
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<tr>
<td>• Comorbid conditions (obesity, infection, renal disease, pulmonary disease, arterial thrombosis)</td>
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<tr>
<td>• Prior history of VTE</td>
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<tr>
<td>• Heritable prothrombotic mutations</td>
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<td>• Pregnancy</td>
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<tr>
<td><strong>Cancer-related factors</strong></td>
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<tr>
<td>• Primary site of cancer (pancreatic, GI, brain, lung, gynecological, renal, hematological)</td>
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<tr>
<td>• Initial 3 to 6 months after diagnosis</td>
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<tr>
<td>• Current metastatic disease</td>
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<tr>
<td><strong>Treatment-related factors</strong></td>
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<tr>
<td>• Recent major surgery</td>
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<tr>
<td>• Current hospitalization</td>
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<tr>
<td>• Active chemotherapy</td>
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<tr>
<td>• Active hormonal therapy</td>
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<tr>
<td>• Current or recent antiangiogenic therapy (thalidomide, lenalidomide, bevacizumab)</td>
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<tr>
<td>• Current erythropoiesis-stimulating agents</td>
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<tr>
<td>• Presence of central venous catheters</td>
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The diagnosis of cancer during pregnancy poses a major burden on the woman and her family. Issues of fetal and neonatal well-being are intricate, while mother's health is of primary concern. With an estimated prevalence of one per thousand pregnancies, cancer is considered to be the second leading cause of maternal mortality behind pregnancy-associated vascular complications. Breast and cervix cancers account for about 50% of pregnancy-related malignancies, followed by lymphoma and leukemia. The mechanisms of thrombosis are escalated in pregnancy. The hypercoagulability state in pregnant women with cancer may lead to placental thrombosis, fetal growth restriction or loss, and VTE.

Pregnant women with ET, PV, and MF are known to be at an increased risk for miscarriages and preterm deliveries. While anagrelide and hydroxycarbamide cannot be recommended during the first trimester, interferon alpha may be safely used in this patient population. The role of antiplatelets in preventing arterial thrombosis has been well-established, and low-dose acetylsalicylic acid (ASA) is therefore recommended in MPN. Low molecular weight heparins (LMWHs) are often used in combination with low-dose ASA; however, the benefit of this combination remains to be determined.

In addition, combined hormonal contraceptives increases the risk of thrombosis and therefore are not recommended in patients with active cancer. Progesterone-only preparations, taken either orally or as an intrauterine device, are probably safe in terms of thrombotic risk.

Risk of VTE is also increased after long-distance travel, which was found to be **3.5-fold higher in females**, mainly due to hormonal contraceptive use. In fact, women with coagulation factor VIII in combination with oral contraception use increased the risk of VTE by over 50-fold in travellers. Behavioural, mechanical, and antithrombotic prophylaxis are recommended in high-risk individuals.
A heparanase procoagulant activity assay is a potential diagnostic innovation that has been tested in various clinical set-ups including end of pregnancy, oral contraceptive use in women, patients with lung cancer, and following orthopaedic surgery. Multicentre collaborations are warranted to advance research in this complicated clinical setting.

Central Venous Catheters and Thrombosis in Patients with Breast Cancer

(Philippe Debourdeau, France)

Long-term central venous catheters (CVCs) are commonly used in patients with cancer, who require infusion chemotherapy and intravenous administration of supportive care treatments. However, the insertion of a catheter may cause a thrombus to form. CVC-related thrombosis (CRT) is most commonly defined as a mural thrombus extending from the catheter into the lumen of a vessel, and leading to partial or total catheter occlusion with or without clinical symptoms.

False CRT (catheter dysfunction without mural thrombus) includes fibrin sheath, which occurs in about 70%
of cases within the first month after catheter insertion, as well as distal tip thrombus. These cases are treated with fibrinolytics. Pinch-off syndrome is another case of false CRT that occurs when the catheter is compressed between the first rib and the clavicle, causing an intermittent mechanical occlusion for both infusion and withdrawal. The evolving risk is a breaking of the catheter leading to its migration to the pulmonary arteries. In this case, removal of the catheter is recommended.

Distinction between true CRT and other causes of catheter dysfunction is important as management differs. True CRT must be treated with anticoagulants, such as LMWH or vitamin K antagonist (VKA).

The number of CRT is growing, as is the number of cancer-treated patients; also, the number of catheters inserted is increasing. The overall incidence of CRT varies depending on the method used; incidence is reported as 27 to 66% for asymptomatic events detected by venography, with a lower incidence of 12 to 18% detected with ultrasound Doppler. Moreover, an incidence of 4 to 5% has been reported for symptomatic events.

CRT represents a major problem in contemporary oncology practice. It may notably lead to pulmonary embolism in 10 to 15% of patients, a loss of the central venous access in 10% of patients, a delay in receiving chemotherapy, and decreased quality of life.

Appropriate treatment of CRT includes:

- Recommended anticoagulation for a minimum of 3 months
  - LMWHs are suggested
  - Oral VKA can also be used, in the absence of direct comparisons of these two types of anticoagulants in this setting
- Keeping the CVC in place if it is functional, well-positioned, and noninfected with good resolution of symptoms under close surveillance

The CAVECCAS (Catheter Veineux CEntral et Cancer du Sein) study is a large prospective study analyzing CRT in breast cancer patients receiving (neo)adjuvant chemotherapy, which is soon to be published.
DEBATE QUESTION 1: Should prophylaxis of VTE with anticoagulation be routinely prescribed for women with locally advanced breast cancer treated with chemotherapy + tamoxifen?

There have only been two clinical trials of VTE prophylaxis in metastatic breast cancer, with conflicting results. In the one study, primary VTE prophylaxis reduced the incidence of VTE; while in the other study, it had no effect. Both studies showed no difference in survival.

Pro (Rupert Bauersachs, Germany)

There is a large amount of evidence showing that tamoxifen increases the risk of VTE in women with breast cancer, particularly in the beginning of treatment. The risk of VTE is increased even further in women receiving tamoxifen in combination with chemotherapy. The Danish Breast Cancer Cooperative Group has shown tamoxifen increases the risk of VTE, particularly in the first few years of treatment and in women over 50 years. The presence of factor VIII mutation also increases the risk of VTE in breast cancer patients treated with tamoxifen. However, data is missing.

Con (Dominique Farge-Bancel, France):

Should we continue tamoxifen in women at risk of VTE or stop? There is no evidence in the literature. The risk of VTE is highest at year 1 and 2, and decreases over time, which is particularly important for a 5-year treatment for these patients. More data and evidence in this population of women is needed.

DEBATE QUESTION 2: Do we need a guidance document specific to women?

Specific clinical scenarios related to women with cancer, aside from pregnancy (in which standard treatment for established VTE and prophylaxis is recommended) are not addressed in current VTE guidelines. There are many unknown questions remaining for women with cancer. As such, symposium faculty, as well as the majority of participants, answered yes to this question.

Current International VTE Guidelines in Cancer Patients include:

- Initial treatment (first 10 days) of established VTE
  - LMWH is recommended, although fondaparinux and unfractionated heparin (UFH) can be also used
- Early maintenance (10 days to 3 months) and long term-treatment (> 3 months) of established VTE
  - LMWH for a minimum of 3 months is preferred over VKAs
  - After 3 to 6 months, LMWH or VKA continuation should be based on individual evaluation of the benefit-risk ratio, tolerability, patient preference, and cancer activity
- Treatment of VTE recurrence with VKA, LMWH, and vena cava filter
  - Three options are recommended:
    - A switch from VKA to LMWH when treated with VKA
    - An increase in LMWH dose when treated with LMWH
    - In some patients, vena cava filter insertion
**Prophylaxis of VTE in surgical cancer patients**
- Use of LMWH or low doses of UFH is recommended; it should be started 12 to 2 hours preoperatively and continued for at least 7 to 10 days
- Extended prophylaxis (4 weeks) after major laparotomy may be indicated in patients with cancer who have a high risk of VTE and low risk of bleeding

**Prophylaxis in medical cancer patients (special focus on lung, pancreatic, and myeloma patients)**
- Prophylaxis with LMWH, UFH, or fondaparinux is recommended in hospitalized medical cancer patients with reduced mobility
- In patients receiving chemotherapy, prophylaxis cannot be recommended routinely
- For patients treated with thalidomide or lenalidomide combined with steroids and/or chemotherapy, VTE prophylaxis is recommended

**Treatment of established CRT**
- Anticoagulant treatment is recommended for a minimum of 3 months
- LMWHs are suggested; VKAs can also be used in the absence of direct comparisons of these two types of anticoagulants
- The CVC can be kept in place if it is functional, well-positioned and noninfected, and there is good resolution under close surveillance

**Prophylaxis of CRT**
- Use of anticoagulant treatment for routine prophylaxis of CRT is not recommended
- CVVs should be inserted on the right side, in the jugular vein, and the distal extremity of the CVC should be located at the junction of the superior vena cava and the right atrium

ITAC-CME developed a clinical tool in the form of a mobile application based on these guidelines, to promote the judicious and appropriate use of anticoagulants as VTE prophylaxis and treatment in patients with cancer.

In conclusion, there are many unanswered questions related to VTE in women with cancer, and participants felt the initiatives on the right would help to improve the outcomes of women with cancer and VTE. This validates the need for continued guidance and future educational initiatives.


This accredited symposium was made possible through an unrestricted educational grant from Aspen Pharmacare.

**References**