

REVIEW ARTICLE

Breast Cancer as an Acquired Thrombophilic State

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Cancer is an acquired thrombophilic condition manifested by increased incidence of venous and arterial thromboembolic complications. Despite progress that has been achieved in treatments over the recent years, thromboembolism remains a major complication in patients with breast cancer; it is accompanied by significant morbidity and mortality. Approximately, 1% of breast cancer patients develop venous thromboembolism within 2 years with the highest incidence occurring in the 6 months post diagnosis. Metastatic disease and their comorbidities are the strongest predictors of the development of thrombotic event. The diagnosis of venous thromboembolism is associated with a higher risk of death within 2 years of diagnosis. Thromboembolic events in cancer patients range from abnormal laboratory coagulation tests without specific symptoms to massive thromboem-

bolism and disseminated intravascular coagulation. The underlying pathophysiology is complex and includes the prothrombotic properties of cancer cells, which can be enhanced by anticancer treatment modalities, such as surgery, hormonal agents, and chemotherapy. Primary thromboprophylaxis in cancer patients should be individualized according to risk. For secondary prevention, several clinical studies have shown that low molecular weight heparin has improved patients' compliance, cancer outcomes and overall survival. This review summarizes the available data on the pathogenesis and clinical approach of hemostatic changes in breast cancer.

Key Words: Blood coagulation, Breast neoplasms, Hemostasis, Thrombosis

INTRODUCTION

Malignancy induces a prothrombotic state, and cancer treatment is often complicated by either venous or arterial thrombotic events. Approximately 15% to 20% of all cancer patients develop thrombosis during the course of the disease. The incidence of cancer-related thrombosis varies according to the primary site, and patients with gynecological and breast cancers are at higher risks of developing venous thromboembolism (VTE) compared with the general population [1].

Breast cancer is the most common type of malignancy in the female population, and 1% of patients experience complications by thromboembolic events during the course of the disease; this further deteriorates patients' clinical conditions and increases morbidity and mortality [2].

The underlying pathogenetic mechanism is complex and involves the activation of a coagulation cascade, the failure of physiological anticoagulant agents and the destruction of

vascular endothelium either by tumor cells or novel therapeutic interventions. Understanding the pathophysiology of the disease in conjunction with clinical, laboratory, and demographic factors is important in identifying patients at high risk. Anti-coagulant drugs in cancer patients are associated with a high risk of bleeding disorders and should therefore involve an individualized prophylactic practice, according to the clinical case and the predictive markers of thromboembolic events.

This study presents an overview of contemporary literature on the epidemiology, clinicopathogenetic mechanisms, treatment, and prophylaxis of thromboembolic complications in breast cancer patients.

EPIDEMIOLOGY

The incidence of VTE after diagnosis of breast cancer has not been accurately determined, as relevant studies differ in diagnostic approaches toward VTE, patient characteristics, and duration of follow-up [2]. There has been a general correlation between VTE and breast cancer therapies. In particular, the higher incidence of VTE has been reported in patients receiving tamoxifen (0.9%), chemotherapy (2.1%) or a combination (4% to 13%), for both early and late stage disease [3]. Conversely, patients with histories of hospitalization for VTE have

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Received: February 7, 2012 Accepted: March 27, 2012

a 1.5 times higher risk of a breast cancer diagnosis within 24 months following the thrombotic episode (odds ratio [OR], 1.78; 95% confidence interval [CI], 1.05-3.20) [4].

The incidence of newly diagnosed VTE cases in breast cancer is not as high as that shown in other cancer types [5]. Chew et al. [2], in a study including 108,255 patients with breast cancer, estimated that the cumulative incidence of VTE was 0.9% and 1.2% in the first and second years, respectively, after diagnosis of malignancy. However, breast cancer is the most common type of cancer in the female population, and the risk of developing VTE is 4.2 times higher in these individuals than in the general population. The higher incidence rate of VTE, 1.2 cases per patient-year, is observed within the first 6 months after diagnosis of malignant disease while, in the second half, the incidence rate was 0.6 cases per patient-year [2].

CLINICAL AND LABORATORY MANIFESTATIONS

A wide spectrum of clinical manifestations of thrombosis may be observed with cancer, ranging from laboratory coagulation abnormalities alone to massive life-threatening thrombosis. About 50% of cancer patients, and up to 90% of patients with metastatic disease, have abnormalities in laboratory coagulation tests, without overt thrombosis. The most common coagulation disorders are mild extension or shortening of prothrombin time or activated partial thromboplastin time (aPTT), thrombocytosis, and increased levels of fibrinogen, fibrin degradation products and D-dimers [6].

Venous events are more common, presented either as deep vein thrombosis (DVT) or pulmonary embolism (PE), together described as VTE. DVT usually affects lower extremities; however, in patients, who have undergone axillary lymph node excision, thromboembolic complications in the upper extremities, implanted ports, and chemotherapy administration devices are also frequent. Other clinical manifestations include migratory thrombophlebitis, non bacterial thrombotic endocarditis (NBTE), thrombotic microangiopathy, and disseminated intravascular coagulation (DIC) [6].

Arterial thrombosis is less common and may be secondary to NBTE. This type of endocarditis is characterized by a prototypic lesion in heart valves, the vegetation, which consists of platelets, fibrin, microcolonies of microorganisms, and scant inflammatory cells. Typically, NBTE does not cause many problems on its own, but parts of the vegetations may break off and embolize to the heart or brain, or they may serve as a focus for bacteria to lodge. Post-mortem studies have shown that this is correlated with underlying malignant disease in 75% of cases. The most common cancer types associated with NBTE are breast, prostate, lung, and large bowel [7].

Idiopathic venous thrombosis can be part of the clinical picture of malignant disease, as patients with idiopathic DVT have a three- to six-fold higher risk of subsequent cancer diagnosis within the next 6 months; however, this is not so frequent in breast cancer [4,8]. In inflammatory breast cancer, presenting symptoms may include swelling in the arm, axillary region, and chest. This might include a venous thrombosis, or a large blood clot; though this is exceptionally rare, it could result from late-stage breast cancer or from undiagnosed inflammatory breast cancer [8].

PATHOGENETIC MECHANISMS OF THROMBOSIS IN BREAST CANCER

The pathophysiology of cancer-related thrombosis is a multifactorial process, and the majority of studies focus on the properties of the tumor cell. However, anticancer therapy causes the release of procoagulant factors and reduced expression of natural inhibitors of hemostasis by tumor cells or macrophages, disrupting the hemostatic balance. Furthermore, surgical procedures and indwelling vascular access devices cause direct damage to vascular endothelium and platelet activation [9].

Pathophysiology of cancer-related thrombosis

In a normal coagulation-fibrinolysis system, there is a natural balance between activation and inhibition of procoagulants and anticoagulants. Cancer cells can alter this balance by mechanisms such as the production of procoagulant and fibrinolytic agents, the release of proinflammatory and proangiogenic cytokines, and direct interaction with the vessels and blood cells through adhesion molecules [9].

The most studied cancer-related procoagulants are tissue factor (TF) and cancer procoagulant (CP). TF is a transmembrane glycoprotein and the primer of physiological coagulation cascade. It is produced by monocytes and vascular endothelium and; is active both in the cell surface and as soluble plasma component. Elevated levels of TF are detected in tumor cells through the activation of oncogenes (e.g., k-ras, MET) and/or the failure of tumor suppressor genes (e.g., p53); they may also be detected in endothelial cells surrounding the tumor, due to secretion of interleukin 1b (IL-1b) and tumor necrosis factor alpha (TNF α) by tumor cells. Genetic alterations related to neoplastic transformation, such as TF, cyclooxygenase 2 (COX-2) and plasminogen activator inhibitor-1 (PAI-1) [10], have been shown to be involved in regulating genes that control hemostasis.

CP, a cysteine protease, is a direct activator of factor X and is encountered only in malignant tissues. CP, with the presence of factor V, can enhance up to three times the production of

thrombin. Elevated levels of CP have been reported in patients with acute promyelocytic leukemia, melanoma, breast, lung, and kidney cancer; however, there is *in vitro* evidence that it is implicated in the metastatic process [11].

Cancer cells can express fibrinolytic proteins, namely tissue plasminogen activator (tPA), urokinase plasminogen activator (uPA), uPA receptor (uPAR) and inhibitors of plasminogen activators-1,-2 (PAI-1, PAI-2). Recent data suggest that these fibrinolytic factors are involved in the development and spread of tumor [12]. Proinflammatory cytokines, such as TNF α and IL-1b, secreted by cancer cells, induce TF expression from monocytes and endothelial cells, reduce the expression of thrombomodulin, a key factor in the protein C pathway [9], suppress the fibrinolytic activity of endothelium and increase the endothelial production of e-selectin and von Willebrand factor (vWF) [11].

The production of vascular endothelial growth factor (VEGF) by cancer cells plays an important role in angiogenesis. VEGF has chemotactic properties for macrophages and induces the expression of TF from monocytes and endothelium. In turn, the expression of TF enhances the expression of VEGF from cancer cells. This correlation between VEGF and TF explains the close relationship between thrombosis, inflammation, growth and metastasis of tumor [13].

Cancer cells have on their surface adhesion molecules that allow their direct interaction with host cells, such as platelets, endothelial cells and leukocytes. Malignant cells that bind to the vascular wall likely play a role in the local induction of coagulation and clot formation, while released cytokines promote leukocyte and platelet adhesion. Fibrin and activated platelets overlap cancer cells and protect them from natural killer cells (NK cells), enhancing their survival [9].

Microparticles are small membrane sections, 0.1 to 1.0 μ m in diameter, released from various cells (platelets, leukocytes, endothelial cells, tumor cells) under conditions of apoptosis and cellular activation. They also have hemostatic action due to the expression of TF, phosphatidyloserin, p-selectin and its ligand (PSGL-1), in addition; to the binding capacities of factors V, VIII, IX, X and prothrombinase complex on them. Elevated platelet microparticles have been described in gastrointestinal and breast cancer. They are involved in the induction of angiogenesis, tumor metastasis, and thrombosis through their phospholipids and TF, while a cancer cell itself may also have particles with a procoagulant phenotype [14,15].

Surgery-related thrombosis in breast cancer

The impact of VTE on women undergoing surgery for breast cancer has not yet been determined. In a study by Andtbacka et al. [16], overall incidence of VTE was 0.16%, per surgery,

within 60 days after a breast operation. This incidence was lower than the figures published by European Organization for Research and Treatment of Cancer (EORTC), where the incidence, including cases of superficial thrombophlebitis, reached 0.8% within 6 weeks after surgery. Without those cases the incidence was 0.3% [17].

Clahsen et al. [17] reported an increased incidence of VTE in women undergoing mastectomy and postmenopausal women (2.3% and 2%, respectively). Other studies found an increasing trend of VTE incidents in surgical procedures of longer duration and complexity, but the increase was not always statistically significant. In most studies, the incidence of VTE after breast surgery increased in advanced stages of disease [16,17].

The damage of vascular endothelium is a mechanism that triggers the development of prothrombotic phenotype, and vascular lesion may be caused by the mechanical local destruction of the vascular wall by the tumor itself, or during surgical interventions, especially in combination with lymph node dissection [18].

Cytotoxic therapy-related thrombosis in breast cancer

In many breast cancer patients, treated with various combined chemotherapy regimens, based on cyclophosphamide or methotrexate or 5-flourouracil, incidence of VTE during treatment was 5% to 7%, and there was no significant difference between regimens [18]. In contrast, during the 2,413-month treatment-free follow-up, no incident of VTE was reported. There is no correlation between treatment-associated VTE and expression of hormonal receptors, patient's age, number of affected lymph nodes, VTE recurrence, and previous history of VTE. The incidence of VTE increased to 18% in women taking cyclophosphamide, methotrexate, 5-flourouracil, vincristine, prednisolone (CMFVP) regimen for stage IV breast cancer [19]. In a randomized study, patients with early stage breast cancer, who received chemotherapy during the perioperative period, had higher risk of VTE within 6 weeks after surgery, compared with patients who did not receive chemotherapy (2.1% vs. 0.6%) [17].

Wall et al. [20] recorded a 1.3% incidence of arterial thrombosis, either cerebral or peripheral, in a series of 1,014 women with stage II and III disease, during chemotherapy. A retrospective study of 2,352 patients showed a significant increase in arterial thrombosis in premenopausal women treated with combined chemotherapy, whereas risk was significantly limited in postmenopausal women treated with either tamoxifen alone or in combination with chemotherapy [21].

The underlying pathophysiology mechanism of thrombotic complications in women with breast cancer, receiving chemotherapy, has not been fully elucidated. The destruction of cells

by chemotherapy and radiotherapy causes the release of procoagulant agents and direct damage to vascular endothelium. In breast cancer patients receiving the regimen cyclophosphamide, methotrexate, 5-fluorouracil (CMF), a significant reduction of protein C, protein S, fibrinogen and factor VII has been observed [22]. The levels of protein C returned to normal after completion of chemotherapy. Other chemotherapy agents can induce the direct expression of TF in macrophages and monocytes, or cause disruption to the vitamin K cycle, reduce protein synthesis in the liver due to inhibition of DNA and RNA in cells and provoke DIC [18]. Angiogenic factors, such as thalidomide, lenalidomide and bevacizumab, have also been associated with an increased risk of VTE, especially in combination with other chemotherapy drugs [9].

However, recent *in vitro* studies report that the antineoplastic drug paclitaxel inhibits platelet aggregation induced by collagen, has antiplatelet activity through inhibition of thromboxane A2 synthase, and reduces the expression of TF in breast cancer cell lines [23,24].

Hormone therapy-related thrombosis in breast cancer

Tamoxifen, either alone or in combination with chemotherapy, is associated with increased risk of thrombosis. In a randomized study of 1,312 patients [25], those receiving adjuvant treatment with tamoxifen have a 2.5-fold higher risk of thrombosis. In a study of Eastern Cooperative Oncology Group (EGOG), the premenopausal women receiving chemotherapy and tamoxifen had significantly more thrombotic complications than those receiving only chemotherapy (2.8% vs. 0.8%, $p=0.03$). Similarly, postmenopausal women undergoing chemotherapy with tamoxifen had more episodes of VTE compared with those receiving tamoxifen alone (8% vs. 0.4%, $p=0.0001$). The incidence of arterial thrombosis was also significantly higher in women undergoing chemotherapy with tamoxifen, compared with those receiving chemotherapy alone (1.6% vs. 0%, $p=0.004$) [21].

There are a number of studies regarding the prothrombotic effects of tamoxifen. Some studies have found a mild reduction in levels of antithrombin (AT) and protein C [18]. Furthermore, some studies have shown that the risk of thrombosis during treatment with tamoxifen is higher in women with FV Leiden mutation and resistance to activated protein C (APCR) [26]. In a small number of patients with breast cancer, there was a decrease of tissue factor pathway inhibitor (TFPI), an increase of APCR, platelet (CD41), and leukocyte (CD45) microparticles during treatment with tamoxifen [27].

Medroxyprogesterone is used in women with metastatic breast cancer, and several studies have demonstrated the prothrombotic action of the agent. Medroxyprogesterone induces

the activation of coagulation, as indicated by measurements of fibrin and thrombin products. The levels of AT, D-dimers, thrombin-antithrombin (TAT) complexes, factor II, factor IX, and plasminogen remained elevated throughout treatment with medroxyprogesterone [18].

Aromatase inhibitors inhibit the synthesis of estrogens from androgens. The risk of VTE during monotherapy with anastrozole is significantly lower, compared with tamoxifen monotherapy (2.1% vs. 3.5%, $p=0.0006$). The risk of thrombosis significantly increases in a case of combination of two factors, compared with tamoxifen monotherapy [28].

Venous catheter-related thrombosis in breast cancer

Several types of central venous catheters (CVC) and venous implants are used in cancer patients, facilitating the administration of drugs and their mobility. The incidence of catheter-related thrombotic events varies greatly among both symptomatic (0.3-28.3%) and asymptomatic (27-65%) patients. Recent studies have reported a reduction of catheter-related VTE, which can be attributed to improved care methods of central venous lines [29].

Catheters can cause endothelial damage and might impede blood flow, while the fibrin sheath generates in about 87% of catheters, as shown on venography within 24 hours of catheter placing. The sheath is then colonized by cocci, but this is not always indicative of subsequent thrombosis [30]. The incidence of intraluminal thrombosis ranges between 13.2% and 93% with a frequency of 0.81 per 1,000 catheter-day [31].

In a study of 300 breast cancer patients [32] with CVC, the incidence of catheter-related thrombotic complications was estimated at 8.3%. All cases were episodes of DVT, although about 6% of cancer patients with arm DVT develop symptomatic PE; asymptomatic PE can be diagnosed by scintigraphy in 11% of cases. Patients with the FV Leiden mutation had a six-fold greater risk of DVT. Furthermore, the study showed significantly higher incidence of DVT in the cohort with advanced metastatic disease, a finding which not confirmed in other studies. Catheter-related thrombosis is a serious complication causing morbidity and delaying anticancer therapy. In a study by Mandalà et al. [32], the median number of chemotherapy cycles in patients experiencing thrombotic complication was significantly lower than in those without DVT ($p<0.001$).

RISK FACTORS OF THROMBOSIS IN BREAST CANCER

Multiple studies have evaluated the risk factors of VTE in cancer patients; these can be categorized according to patient

characteristics (i.e., age, gender, race, comorbidities), cancer properties (i.e., stage, primary site), treatment modalities (i.e., surgery, hospitalization, chemotherapy, supportive care), while several biomarkers, such as platelet count, leukocyte count, TF expression, soluble p-selectin, D-dimers, and C-reactive protein may be predictive of cancer-related thrombosis [1].

Important risk factors for VTE, within the first two years after diagnosis of breast cancer, include: age > 75 years (hazard ratio [HR], 2.0 vs. age < 45 years), the number of coexisting chronic diseases (HR, 2.9 if ≥ 3 vs. 0), and metastatic disease (HR, 6.3 vs. localized disease). Interestingly, Asian race and breast surgery have been associated with a lower probability of VTE. Surgical interventions have been implicated in 9% of VTE cases in breast cancer and patients undergoing surgery had a 400 times lower risk of VTE, compared to the adjusted cohort who did not have the surgery [2]. Similar results have been published for patients with colon cancer [33]. These results may be attributed to the exclusion of patients with advanced metastatic disease or comorbidities from major surgical procedures [2].

Several studies have assessed the role of menstrual status, body mass, number of affected axillary lymph nodes, expression of hormone receptors, type of surgery, and breast cancer histology in developing VTE. VTE risk during chemotherapy was significantly higher in postmenopausal women (HR, 2.01; 95% CI, 1.09-3.70; $p = 0.002$), women with increased body mass index (body mass index [BMI] > 25 kg/m² HR, 2.92; 95% CI, 1.71-5.82; $p < 0.001$), and women with previous mastectomy (HR, 3.57; 95% CI, 1.88-6.79; $p < 0.001$). The number of affected lymph nodes, histological type of disease, and expression of hormonal receptors were not risk factors for VTE. The preexisting-hemostatic disorders, such as increased APCR, presence of antiphospholipid antibodies, elevated D-dimers, TAT complexes, and prothrombin fragments F1+2, may be risk factors during chemotherapy or after mastectomy [18].

In breast cancer, microparticles are significantly elevated in advanced stages compared with *in situ* carcinoma or benign breast diseases; 82.3% of them have a platelet origin (CD61) [34]. Studies regarding factors in women with breast cancer, and benign breast diseases, found a significant increase in levels of VEGF (seven-fold), angiopoietin ([Ang-1], 50% higher), angiopoietin receptor ([Tie-2], two-fold), vWF and plasma viscosity [35]. According to findings concerning the early hemostatic changes in women receiving chemotherapy, patients who developed VTE had consistently elevated levels of fibrinogen, D-dimers, TF, and VEGF before and after chemotherapy [36].

PREVENTION AND TREATMENT OF THROMBOSIS

Thromboprophylaxis in breast cancer

There are two main forms of perioperative thromboprophylaxis: 1) mechanical, which involves calf stimulation, intermittent pneumatic compression devices, graduated static compression stockings, and venous foot pump devices; and 2) pharmacologic, including unfractionated heparin (UFH), low molecular weight heparin (LMWH) and oral anticoagulants. The administration of thromboprophylaxis in breast cancer increases the risk of postoperative hematoma and bleeding. In particular, 11% to 18% of women receiving LMWH, while only 7% of patients under mechanical thromboprophylaxis, present with hemorrhagic complications [16].

Given the relative low incidence of VTE in breast cancer, most studies suggest a mechanical perioperative prophylaxis. In addition to early mobilization, the use of tight socks should not be omitted, even in low-risk surgery; it should be continued throughout hospital stay. It is recommended that the discontinuation of tamoxifen either before any surgery, or in immobilized patients until full mobilization [18].

According to a randomized controlled trial, thromboprophylaxis with low dose warfarin (international normalized ratio [INR] range, 1.3-1.9) was effective and safe in reducing the incidence of thrombosis in women, receiving chemotherapy, with stage IV metastatic breast cancer. However, the need for laboratory monitoring of patients receiving warfarin has not allowed its use on a large scale [3]. Systemic thromboprophylaxis is not recommended for all patients receiving cytotoxic or hormonal therapy. Generally, thromboprophylaxis is recommended 1) during chemotherapy after mastectomy in postmenopausal women with increased BMI (> 25 kg/m²) and preexisting coagulation disorders, 2) in the presence of long-term CVC, 3) in congenital thrombophilia (e.g., FVLeiden, AT deficiency), 4) in positive VTE history, 5) in a combination of above states.

The anticoagulant modality includes LMWH or low-dose warfarin, which is begun 3 to 4 days before chemotherapy and is continued throughout cytotoxic therapy [18]. There is relatively little data about the incidence of thromboembolism in patients undergoing radiotherapy. The radiation can lead to endothelium damage, which in turn may activate the platelets and the clotting mechanism. Thus, in high risk patients, the use of thromboprophylaxis should be discussed.

In cases where the use of tamoxifen is contraindicated due to its thrombogenic properties, administration of third generation aromatase inhibitor, such as anastrozole, should be considered; the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial resulted in a significant reduction of venous thrombosis

[28]. Currently, however, all pharmaceutical agents used in endocrine therapy or chemoprevention of breast cancer, including aromatase inhibitors, correlate with an increased risk of thromboembolic events.

The use of thromboprophylaxis in patients with CVC has not been established and is not applicable in practice. Thrombus formation can not be avoided despite regular care of the catheter with heparin. Fibrinolytic agents, such as streptokinase and urokinase, can be used to dissolve the occlusion of catheters [29].

Treatment of acute cancer-related thromboembolism

The standard treatment regimen for thrombotic events consists of an initial phase with UFH or LMWH, followed by a long-term phase with vitamin K antagonists (VKA). This two-phase treatment approach provides an immediate anti-coagulant effect while waiting for VKA action. Multiple randomized trials have confirmed that LMWHs are at least as efficacious as UFH in reducing recurrent thrombosis, bleeding complications and 3-month mortality; they also appeared to have an advantage against coumarin anticoagulants in cancer patients [37].

In a cancer patient population, warfarin is associated with increased risk of bleeding and recurrent VTE. Moreover, several other problems, such as thrombocytopenia, medication, invasive procedures, infections, malnutrition, and hepatic dysfunction, may influence the anticoagulant therapy and lead to closer coagulation monitoring; often, it leads to treatment discontinuation. In the CLOT trial [38], 602 cancer patients with documented VTE were randomly assigned to receive either dabigatran or dabigatran followed by VKA, for 6 months. Recurrent VTE occurred in 9% of patients in the dabigatran group, compared to 17% in the second group.

These data have established LMWH, for at least 3 to 6 months, as the standard care for cancer-related thrombosis, as recommended by the American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN), European Society of Medical Oncology (ESMO), and other guidelines [39]. The optimal duration of VTE treatment in breast cancer patients has not been accurately determined. Generally, heparin is administered in cases of active malignant disease and throughout cancer treatment [16].

In symptomatic patients with acute CVC-related thrombosis, such as limb pain and swelling, it is often necessary to administer long-term anticoagulation therapy. Catheter removal is not necessary at the initial phase and is reserved for cases of catheter malfunction, extension of thrombosis, and persistent pain or inflammation [18].

Future perspectives in anticoagulation therapy

Heparins and VKAs have been the mainstay of anticoagulant

therapy for over 50 years. There are data for UFH, LMWH, fondaparinux and warfarin for primary prophylaxis, but contemporary studies focus on LMWH in a population of cancer patients. A new generation of anticoagulants are available or under development, and these offer a favorable balance of anticoagulation to hemorrhagic effects. One phase II study [40] evaluated apixaban in outpatients receiving chemotherapy, and a new ultra LMWH (AVE5026) [41] showed a favorable safety-to-efficacy ratio, being suitable for cancer patients at increased risk of both bleeding and VTE. Dabigatran and rivaroxaban are orally administered drugs effective in reducing VTE incidence in orthopedic surgery [42].

The novel drugs are of significant interest in cancer patients as they are orally administered and do not require systemic laboratory monitoring. However, cancer patients with thrombotic complications are a special population, and they substantially differ from non-cancer patients with thrombosis. Thus, larger randomized trials are needed in order to prove the efficacy and safety of new anticoagulation agents in the oncology setting.

EFFECT OF THROMBOTIC COMPLICATIONS ON SURVIVAL IN BREAST CANCER

In a recent study of 134 women with breast cancer, in patients with VTE, the 28-day mortality rate was 15%; in those with symptomatic VTE, the 28-day mortality was 22% [43]. In another study, the overall survival of breast cancer patients with VTE was 27.4 months and dropped to 6.2 months in those with metastatic disease [44].

Significant predictive factors of death in the first 2 years after the diagnosis of breast cancer were advanced age, African-American race, advanced cancer stage, and number of chronic diseases. Undifferentiated carcinoma was associated with a higher risk of death compared with breast adenocarcinoma (HR, 2.4; 95% CI, 2.2-2.5). The risk of death in patients with VTE increased in the second half of the first year and the second year since the diagnosis of cancer [2].

In adjusted groups for age, race, number of comorbidities and histology, the most important risk factor for death within 2 years of the cancer diagnosis was VTE (HR, 2.3; 95% CI, 2.1-2.6). This finding was reported for all stages but was more prominent in patients with localized disease (HR, 5.1; 95% CI, 2.1-2.6) [2]. Similarly, a randomized study has found that LMWH in cancer-related VTE offers survival advantages in patients with less advanced disease [45].

Several studies have indicated a survival benefit in patients receiving LMWH or UFH, a fact that does not simply result from a decrease in the incidence of VTE but also from poten-

tial antineoplastic properties of heparins. However, subgroup analysis showed that heparins improved survival in certain cancer populations. Further investigation is needed to fully characterize this effect and how it is affected by different cancer types and stages. Thus, current guidelines do not recommend the use of primary thromboprophylaxis to offer a survival advantage in cancer patients [42].

CONCLUSION

Despite the lower incidence of thrombotic complications in breast cancer compared with other malignancies, breast cancer patients are at higher risk compared with the general population. The number of patients who have complications is considerable given the high incidence of breast malignancies in the female population worldwide. The estimated incidence of VTE among breast cancer patients is approximately 1%, and most thrombotic episodes occur within the first year of diagnosis of malignant disease. This finding can be attributed both to the application of interventional therapeutic practices and to active biological behavior of a tumor that induces a procoagulant state.

Cancer-associated thrombosis is related to an altered balance between coagulation and the fibrinolytic system, due to tumor cell properties. Medical interventions, such as cytotoxic therapy, hormonal agents, breast surgery, and venous catheters lead to vascular damage and activation of cellular and plasma factors that enhance the hypercoagulable state.

Symptomatic thrombotic events in breast cancer patients usually manifested as DVT both in lower and upper extremities, especially in preceding surgical procedures and presence of long-term venous devices. About 50% of cancer patients do not develop symptomatic thrombosis, despite the laboratory abnormalities, a fact that may lead to underestimation of the frequency of this complication. The coagulation laboratory assessment is often indicative of a hypercoagulable condition, although the clinical utility of thrombotic biomarkers is not yet established.

The risk of VTE in breast cancer varies according to age, number of comorbidities, cancer stage, BMI and menstrual status. VTE risk further increases in cases of chemotherapy and hormonal therapy. Thrombotic complications in breast cancer provoke the deterioration of their performance status, impede treatment administration, and limit survival. Notably, VTE is regarded as the most important risk factor for death within 2 years of cancer diagnosis.

Mechanical perioperative prophylaxis, along with early mobilization, is suggested in most studies of breast cancer patients; this is to lower bleeding risk. However, current guide-

lines support the use of anticoagulation in high-risk cancer patients, although there is limited guidance concerning type and duration. In the setting of primary prophylaxis, LMWH is at least as effective as UFH. In addition, the pharmacokinetic properties of LMWHs facilitate their use with reduced hospital visits and the need for coagulation monitoring. LMWH is also recommended for secondary prophylaxis; compared with warfarin, it displays increased efficacy and a good safety profile.

Improving patient outcomes depends on identifying high risk patients who might benefit from primary thromboprophylaxis. Further studies are needed to establish the predictive role of coagulation abnormalities in breast cancer and the potential antineoplastic effects of anticoagulants. Understanding the pathophysiology of cancer-related thrombosis may allow the development of clinically applicable risk score and use of target strategies.

CONFLICT OF INTEREST

The author declares that there no competing interests.

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