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Approach to Chemotherapy-associated Thrombosis

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Introduction

Venous thromboembolism (VTE) is a common source of morbidity and mortality in the setting of malignancy, with the potential to present at the time of diagnosis, throughout treatment, and ultimately as a frequent cause of death.[1] It has been well established that the diagnosis of malignancy itself is a potent risk factor for the development of deep vein thromboses/pulmonary emboli with several malignancies including, but not limited to, pancreatic, gastroesophageal, lung, and brain cancers demonstrating a particularly increased risk. [23] The risk for VTEs in patients with cancer has been estimated at 4-7.5 times greater than that for the general population. [4]

Several contemporary studies have investigated independent predictors for VTEs in patients actively receiving chemotherapy leading to the development of risk models for identifying patients at highest risk. [5] The Khorana model is a validated scoring system that utilizes specific patient characteristics and laboratory values to stratify patients into low, intermediate, or high risk for venous thromboembolism; this model was developed in a study population of 4,066 cancer patients that were initiated on chemotherapy. The patients were observed for a median period of 2.5 months. In this model, five variables including site of primary cancer, prechemotherapy platelet count greater than 350×10^9/l, prechemotherapy leukocyte count greater than 11×10^9/l, hemoglobin less than 10g/dl, and BMI of $35 kg/m^2$ were identified as quantifiable risk factors increasing the likelihood of developing symptomatic VTEs.[6] Each variable was assigned a numerical value ranging from 0-2 and patients were stratified into three categories based on the total score obtained from the variables. The conclusion from this study was that patient in the low (score = 0) and intermediate (score = 1-2) risk group had a low incidence of VTE and would most likely not benefit from thromboprophylaxis. In contrast, Khorana et al observed that patients identified in the high risk group (score ≥ 3) had a higher risk of VTE and hence would most likely benefit from initiation of thromboprophylactic therapy. It is important to note that this group of patient (i.e. high risk scores) were a minority of the patients studied. This study mainly included patients with good performance status and did not adequately represent certain

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malignancies that are associated with a higher risk for VTE e.g. central nervous system malignancies.[7]

Subsequent models such as the Vienna VTE Risk Assessment Score have proposed that the inclusion of other biomarkers such as the D-dimer and the cell adhesion molecule soluble P-selectin could further enhance one's ability to predict thrombosis risk. [78] In fact, a host of other potential biomarkers for thrombosis risk have been investigated with preliminary data suggesting that elevated clotting factors, markers of inflammation, and procoagulant tissue factor associated microparticles (derived from the endothelium or cancer cells themselves) may all contribute to the underlying pathogenesis of cancer related VTEs; these biomarkers and their potential role in predicting risk of thrombosis in the cancer patient have been recently reviewed in detail elsewhere.[9]

Despite the fact that evidence has supported a causal relationship between chemotherapy and thrombosis for over three decades, it remains an underappreciated risk that has not been routinely incorporated into thrombosis risk assessment models.[10] By the early 1980s, studies in women with breast cancer had demonstrated this increased risk of thrombosis in both the adjuvant setting and in metastatic disease. [11-12] In patients undergoing multidrug therapy for metastatic breast cancer (cyclophosphamide, methotrexate, 5-fluorouracil, vincristine, and prednisone), 17.6% developed thrombosis while on treatment, a majority of these being VTE, compared to just over 2% while receiving no therapy.[10]

Below we review specific anti-neoplastic drugs, both cytotoxic and targeted agents, that have been associated with an increased thrombotic risk and the proposed mechanisms for thrombosis. We conclude with a discussion of the implications for VTE prophylaxis and future considerations to reduce the risk of DVTs/PEs in the cancer population.

Cytotoxic Chemotherapy

Cisplatin

Cisplatin is a fairly ubiquitous chemotherapeutic agent, used in various combinations to treat a wide variety of malignancies. An appreciation of the increased vascular toxicity and thrombotic potential of cisplatin based therapies was noted not long after its FDA approval in 1978 for the treatment of testicular and ovarian cancers. [13] Increased indications for cisplatin-based treatments were associated with a concomitant rise in thrombotic events (both arterial and venous) that occurred in patients exposed to this chemotherapeutic agent. [1415] Perhaps most telling is the marked increased in thrombotic events in patients treated with cisplatin compared to patients treated with other platinum based regimens. In the REAL-2 trial, 15.1% of patients treated with ECF (epirubicin-cisplatin-5FU) experienced some form of thromboembolic event during treatment, compared to 7.6% in patients randomized to EOX (epirubicin-oxaliplatin-capecitabine). [16]

Such observations led to a large, single institution retrospective investigation of all thromboembolic events (TEE) in patients treated with a cisplatin-based regimen. This study demonstrated a TEE in 18.1% of patients either actively receiving cisplatin or having had completed cisplatin based therapy within the preceding four weeks, with over 90% related to

venous thromboembolism.[17] A subsequent meta-analysis of 38 phase II and III trials comparing cisplatin verse non-cisplatin treatments also demonstrated a significantly increased risk of VTEs in the cisplatin treated groups (RR=1.67, P=0.01). Notably, there was a marked variability in the incidence of VTEs among the trials included in this meta-analysis ranging from 0 to 17% in patients treated with cisplatin. [18]

The mechanism of cisplatin induced hypercoagulability has not been precisely defined. In a small prospective study of thirteen patients treated with cisplatin, three developed arterial thrombosis. All of these three patients had elevated von Willebrand factor (vWF) levels prior to initiating cisplatin; vWF levels increased even further after cisplatin therapy to greater than 600% of normal.[19] In addition, Lechner et al demonstrated in vitro that cisplatin-induced endothelial cell apoptosis results in the release of procoagulant endothelial microparticles that are able to generate thrombin through tissue factor independent pathways. [20]

L-asparaginase

L-asparaginase is incorporated into induction regimens for the treatment of pediatric and adult acute lymphoblastic leukemia (ALL). L-asparaginase depletes intracellular asparagine and leads to decreased protein synthesis and subsequent cellular apoptosis. Early case reports documented an increased incidence of both thrombotic and hemorrhagic complications in the setting of L-asparaginase treatment. In a multicenter review of pediatric patients treated with asparaginase containing regimens between 1976-1980, 18 children of the 1547 studied developed a ‘severe’ thrombotic or hemorrhagic complication; 14 of these involved CNS events: 5 intracranial thromboses, 5 intracranial hemorrhages, and 4 with intracranial thrombosis with hemorrhagic conversion. [21] The risk of thrombotic complications in the adult population treated with asparaginase is also markedly elevated; retrospective data has demonstrated a 4.2% incidence of thrombosis in adults with ALL during induction therapy. [22] While the quintessential TEE associated with asparaginase therapy is intracranial dural sinus thrombosis, there is also a marked increase risk of venous thrombosis of the extremities, in particular central venous catheter related clots. [23]

The thrombotic tendency seen in patients treated with asparaginase appears to be related to depletion of key proteins in the regulation of the coagulation pathway. In a series following daily plasma levels of protein C and S after initiating asparaginase therapy, protein C levels dropped to 30% of normal by days 6-10 of therapy, and protein S dropped to 41% by days 11-12. [24] Even more fundamental to the prothrombotic state, the synthesis of plasminogen and antithrombin (AT) is markedly impaired with asparaginase based therapy.[2526] The net effect is increased thrombin generation with impaired thrombin inhibition.

Fluoropyrimidines

5-Fluorouracil (5FU) features prominently into the treatment of gastrointestinal malignancies and has demonstrated activity against several other cancers, including breast and head and neck. The most feared cardiovascular complications of 5FU and its oral prodrug capecitabine are related to direct cardiac toxicity which can manifest as angina or even true myocardial infarction. The incidence of fluoropyrimidine induced cardiac toxicity

has been estimated between 4.2 to 19% with a noted increased risk in the setting of higher doses and continuous infusions; while the effects are usually reversible after cessation of the drug, there have been case reports of fatal outcomes. [2728] It is worth noting that fluoropyrimidine induced angina or ischemia is not due to coronary artery thrombosis, but is more likely related to arterial vasospasm or direct myocardial toxicity from metabolites of 5FU. [2829]

There is only limited evidence that 5FU increases the risk of VTE. Retrospective data in patients treated with 5FU and leucovorin for colon cancer demonstrated an incidence of VTE as high as 15%. [9] In a phase I clinical trial, 5FU in combination with G-CSF reached VTE rates of 29%.[30] However, these rates are significantly higher than reported in most other trials. For example, Tournigand et al randomized 220 patients to sequential FOLFOX (5FU, leucovorin, oxaliplatin) followed by FOLFIRI (5FU, leucovorin, irinotecan) or the reverse sequence, and only 2 patients (one in each arm) developed symptomatic VTE in the form of PEs. [31]

The degree to which 5FU itself causes VTE therefore remains somewhat uncertain; laboratory data would at least suggest that 5FU does contribute to a potentially prothrombotic environment through the depletion of protein C and increased thrombin activity. [3233] Furthermore, animal models and human endothelial cell cultures exposed to 5FU demonstrated endothelial cell damage with the potential to promote thrombus formation. [3435]

Targeted Agents

Tamoxifen and Aromatase Inhibitors

The connection between tamoxifen and increased risk of thrombosis has been recognized since the 1970s and the start of its use in breast cancer treatment.[3637] Data from the Fisher trials for adjuvant treatment of local breast cancer identifies a relative risk (RR) of 4.0-6.0 in the 5-year setting and 3.25 in post 5-year setting[38-40]. Saphner evaluated data from 7 ECOG trials from 1977-1987 to further emphasize tamoxifen's relation to thrombosis. Premenopausal women that received tamoxifen and chemotherapy had an increased risk of venous and arterial thrombosis versus chemotherapy alone (2.8% vs 0.8%, 1.6% vs 0.0% respectively) [41]. Comparisons looking at race show no difference in RR and mirror data from prior studies; RR of 2.17 and 3.19 in African American and White women treated with tamoxifen, with chemotherapy plus tamoxifen increasing to 10.70 and 15.49 respectively[42]. Interestingly, a Danish trial looked at the time course for the occurrence of these events in the adjuvant setting. As described in their analysis, the highest risk is during the first two years (adjusted RR of 3.8) with a non-significant increased risk in years 3-5 of therapy (adjusted RR of 1.8)[43].

In contrast to tamoxifen, aromatase inhibitors (AI) have not been shown to increase the risk of thrombosis, although data in the immediate adjuvant setting is limited to comparisons between tamoxifen and AIs. The ATAC trial data showed a RR of 2.0 with tamoxifen and anastrazole versus anastrazole alone and a RR of 1.7 with tamoxifen versus anastrazole[44], indicating that the thrombosis risk was most likely related to tamoxifen use. When looking

at the “switch” trials in which patients were started on tamoxifen then changed to AI versus placebo, no increased risk of thrombosis was noted while patients were on AIs[45,46] to further suggest that AIs are not associated with an increased risk for thrombosis.

Over the past two decades, there has been several options added to the oncologist's armamentarium, each with their unique adverse effects. Specifically when looking at venous thrombosis, of these new agents, two classes come to the forefront: VEGF inhibitors and immunomodulatory drugs.

Antiangiogenic Agents

The first approved by the FDA was bevacizumab in use for colon cancer, glioblastoma, and non-small cell lung cancer (NSCLC). This agent is a monoclonal antibody directed at vascular endothelial growth factor A (VEGF-A), which is released by malignant cells to activate the endothelium. Once activated, matrix metalloproteinases break down the extracellular matrix and allow for new vessel growth and subsequently continued tumor growth[47].

Since its release, there have been discrepancies in the toxicities of this agent, with respect to thrombosis. Kabbinavar reported 23% in the treatment arm vs 6% in his control arm in the use of bevacizumab with 5-FU and leucovorin in metastatic colon cancer[48]. Contrary to this, Hurwitz in 2004 and Kabbinavar in 2005 showed no difference between the treatment arm and control arm in patients with metastatic colon cancer[49,50]. Subsequent meta-analyses have also drawn different conclusions about bevacizumab and risk of venous thromboembolism. Nalluri, et al looked at 7956 patients from 15 trials and reported a RR of 1.33 in both all-grade (11.9%) and high-grade VTE (6.3%)[51]. Another meta-analysis pooled 1745 patients from three trials showed no difference in overall rate of VTE (HR 0.89) but an increased risk of arterial thrombosis (HR 2.0)[52].

The first of the oral tyrosine kinase inhibitors (TKI) that targeted VEGF, semaxanib, was never brought to market due to its vascular toxicity profile. In a Phase I trial with gemcitabine and paclitaxel, 8 of the first 19 patients suffered from a VTE event[53]. When evaluated in vitro, studies showed increased thrombin potential, E-selectin, von Willebrand factor, and soluble tissue factor. When combined with gemcitabine and cisplatin, this led to a concomitant activation of the coagulation cascade. They hypothesized that the endothelium, becoming starved of VEGF, activates and upregulates these molecules. In this state, it also becomes susceptible to the endothelial damage induced by cytotoxic therapies, leading to thrombosis[54]. Additionally, studies have shown an elevation in VEGF during thrombus resolution[55]. Over expression in the presence of a thrombus leads to increased neovascularization and recanalization[56]; two actions intrinsic to thrombus resolution. This suggests that VEGF targeted therapy is also associated with decreased thrombus resolution.

Other oral VEGF inhibitors are now available: sorafenib, sunitinib, pazopanib, vandetanib, and axitinib. These agents are broader in their targets than bevacizumab. Sunitinib for example affects VEGF receptor s-1, -2, -3, cKIT, Fms-like tyrosine kinase 3 (FLT-3), colony stimulating factor 1 receptor (CSF-1R), and RET. Sorafenib has similar targets but includes platelet derived growth factor receptor beta (PDGFR-β). In contrast to semaxanib,

these agents have not been associated with increased risk of VTE. Two meta-analyses recently published cite a relative risk of 0.91 and 1.1 in comparison to non-TKI arms[5758]. These agents, however, have been used as monotherapy for the time being in malignancies traditionally not known for thrombosis risk. In the future, combination therapy may reveal an increased thrombosis risk, much like thalidomide and other immunomodulatory agents, where the cytotoxic therapy induces thrombosis which is propagated by VEGF blockade. For example, Evans specifically looked at axitinib and its role in inhibiting thrombus resolution. They showed that the agent had no effect on initial thrombus generation as no difference in early fibrillar collagen content (a marker of thrombus organization), thrombus volume, neutrophil content, or recanalization was evident against a control. By day 17, there was significantly less of the aforementioned except for neutrophil count in the axitinib treated model. The natural progression of macrophage accumulation in thrombus was significantly impaired, which follows from VEGFR1 inhibition on macrophages[59].

Immunomodulatory Agents

It is well known that multiple myeloma (MM), along with MGUS, is a prothrombotic state. Interestingly enough, IgA and IgG MGUS carries an increased thrombosis risk but IgM does not[60]. Multiple myeloma creates an inflammatory cytokine milieu with elevated levels of TNF, CRP, and IL-6 [61]. IL-6 in particular has been shown in vitro to trigger the coagulation cascade[62]. Other pathways have been presented as possible etiologies for this prothrombotic state, including a transitory acquired activated protein C resistance outside of Factor V Leiden related to disease activity[63].

As a single agent, the risk for thrombosis with thalidomide in the treatment of multiple myeloma is not clearly increased, roughly 3-4%[64]. The use of thalidomide saw an increase in the incidence of VTE only once combined with other agents. Zangari did an up-front randomization to thalidomide or no thalidomide with anthracycline-based induction chemotherapy in newly diagnosed MM, citing a 28% versus 4% incidence of VTE[65]. In another multi-center trial looking at melphalan, prednisone, and thalidomide versus melphalan and prednisone alone in an older patient population, the incidence was 17% vs 2%[66]. This increased risk also occurs in patients receiving only steroids and no cytotoxic agents, as described by Rajkumar where the incidence was 17% with thalidomide/ dexamethasone and 3% with dexamethasone alone[67].

These effects are shared with the second generation agent lenalidomide. Similarly to thalidomide, when used as monotherapy the rates of thrombosis are not elevated (1% when used in MDS[68], 4% when used in MM without thromboprophylaxis[69]). When used in conjunction with dexamethasone, this rate rises to approximately 11-14% prior to the use aspirin thrombophrophylaxis[7071]. After the utilization of thromboprophylaxis, this rate fell to 1-3%[72]. Additionally, the dose schedule of the dexamethasone with the lenalidomide changes the endothelial manifestations with pulse steroids leading to greater variation in fibrinogen, P-selectin, and VEGF than weekly dexamethasone[73].

Limited data exists on pomalidomide and thrombosis. In one Phase I trial of pomalidomide monotherapy not using thromboprophylaxis, 4 out of 32 patients developed VTE[74]. While this number is greater than that cited with other agents, the number of patients limits

interpretation. A subsequent trial using pomalidomide with or without dexamethasone had rates of 2% and 3% respectively with all patients receiving thromboprophylaxis[75].

This requirement of a second agent is similar to the anti-VEGF agents. Thalidomide and its brethren likely precipitate platelet adhesion and thrombosis by maintaining endothelium in a VEGF-starved state, unable to recuperate after cytotoxic chemotherapy induced vascular injury[76]. Other theories have been proposed. Kaushal et al proposed that thalidomide increases the expression of protease-activated receptor 1[77]. PAR-1 is expressed on both platelets and endothelium. It presents its own ligand, which is irreversibly unmasked by thrombin. This leads to platelet activation, granule secretion, and aggregation. On the endothelium, PAR-1 facilitates platelet and neutrophil rolling and adhesion. Therefore, PAR-1 may serve as the connection between injury and the coagulation response[78]. Abdullah et al noted that thalidomide leads to conformation changes in GPIIb/IIIa via increased target for PAC-1, indicating platelet activation[79], and further reinforcing the importance of platelet activity in thalidomide related thrombosis.

Supportive Agents

Corticosteroids

Steroids play a fundamental role in the supportive care of the cancer patient and are regularly incorporated into treatment protocols for hematologic malignancies (i.e. lymphoma, multiple myeloma). An association between corticosteroid excess and increased risk of thrombosis was noted outside the field of oncology over sixty years ago; natural history studies of patients with Cushing's Syndrome noted a relatively high rate of pulmonary emboli in a series of patients published in 1951.[80] Increased risk of VTE secondary to exogenous steroid use was recently confirmed in a large case control study which included patients with malignancy; this study demonstrated an incidence rate ratio of 2.31 for DVT/PE in patients actively taking corticosteroids compared to controls.[81]As noted above, steroids in combination with immunomodulatory derivatives in the treatment of myeloma result in profoundly increased risks for VTEs. In addition, the use of high dose steroids (>/= 80mg dexamethasone per treatment cycle) for antiemetic purposes resulted in a significantly increased rate of VTEs (OR = 3.47, 95% CI: 1.2-10.3). [82]

Mechanistically, corticosteroid use has been shown to increase circulating levels of clotting factors VII, VIII, XI and fibrinogen in healthy volunteers. [83] Further, studies of patients with Cushing's syndrome demonstrated increased clotting factors as well as evidence of decreased thrombolysis associated with increased plasminogen and alpha-2 antiplasmin levels. [84]

Hematopoietic Growth Factors

Erythropoietin stimulating agents (ESAs) are used to increase hemoglobin levels and decrease the total number of transfused red blood cells in cancer patients undergoing myelosuppressive chemotherapy. ASCO guidelines recommend discussion of the risks and benefits of ESAs when hemoglobin levels drop below 10g/dl in this setting. [85] Multiple studies have demonstrated an increased risk of VTE, and a recent Cochrane review demonstrated that ESAs resulted in a relative risk of 1.52 for the development of VTEs (CI

1.34-1.74). [86] There has been some suggestion that this risk is reduced when ESAs are held until hemoglobin is less than 10g/dl, but this data is weak and not reproduced in other studies. [8687] The prothrombotic nature of ESAs in the oncology patient is not likely due to elevated hemoglobin levels but is rather multifactorial; erythropoietin has been shown to decrease proteins C and S, increase PAI-1 production, and increase platelet activation. [88]

Granulocyte colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) are used to aid granulocyte cell recovery after myelosuppressive chemotherapy. Prospective data has demonstrated that the use of white cell growth factor is associated with a significant risk of VTE (OR = 2.09, CI: 1.2-3.6) [5] In healthy patients treated with G-CSF prior to stem cell collection, markers for increased clotting activity (prothrombin fragment F1+2, thrombin-antithrombin complex, and D-dimer) were all elevated after exposure to G-CSF. In addition, G-CSF use resulted in some evidence of endothelial cell damage/activation with increased serum levels of thrombomodulin and von Willebrand factor. [89]

Prophylactic therapy

Several studies have investigated the role of VTE prophylaxis in the ambulatory oncology patient. Two large clinical trials, the PROTECHT and the SAVE-ONCO trials, randomized patients with solid tumors to prophylactic dose low molecular weight heparins (LMWH) versus placebo. The PROTECHT study included 1150 patients actively receiving chemotherapy for lung, gastrointestinal, pancreatic, breast, ovarian, or head and neck cancers with the treatment group receiving the LMWH nadroparin; prophylactic nadroparin decreased the incidence of symptomatic arterial or venous thrombosis from 3.9% in the placebo group to 2.0% in the treatment arm ($p = 0.02$). [90] At the same time, the risk for minor bleeds was similar in both treatment and placebo groups with only a slightly increased risk for major bleeds (0.7% versus 0 in the placebo group). Similarly, the SAVE-ONCO trial included 1608 patients with locally advanced or metastatic solid tumors undergoing chemotherapy with patients randomized to the LMWH semuloparin vs placebo; again, the treatment arm demonstrated a statistically significant decrease in the primary end point of VTE/VTE related death (3.4% v. 1.2%; $p < 0.001$). [91] Several other smaller trials investigating VTE prophylaxis in patients undergoing treatment for specific malignancies (pancreas, lung, breast, glioma) have been performed with mixed results. [92-94] While the SAVE-ONCO and PROTECHT studies were statistically positive, the results must be interpreted with caution. First, the rate of thrombosis in the control arm was fairly low in each trial (<5%), which suggests that the percentage of patients in these largely unselected populations that could benefit from prophylactic therapy is quite small. Second, one must appreciate that there was no suggestion that prophylaxis in the treatment groups had any impact on overall survival and that the only major bleeding events occurred in the treatment arms. Again the risk of major bleeding was quite small and not statistically significant, but does serve as a reminder that any intervention comes with potential costs. It is worth emphasizing that the FDA has not approved any drug with the indication of VTE prophylaxis in solid tumor patients undergoing systemic chemotherapy. ASCO guidelines have been recently updated regarding VTE prophylaxis in patients with solid tumors undergoing treatment; based on available data, the expert panel did not recommend routine

thromboprophylaxis in cancer outpatients, but stated that it could be considered in a 'highly selected' population. [95]

Exceptions to this recommendation are patients with multiple myeloma undergoing thalidomide or lenalidomide-based treatments. Current ASCO guidelines do recommend thromboprophylaxis with aspirin or LMWH in this clinical situation. As previously noted, patients with myeloma treated with a thalidomide/lenalidomide regimen are at an exceptionally increased risk for VTEs. Early studies demonstrated that prophylactic doses of LMWH significantly reduced the incidence of VTEs.[96] The choice of prophylaxis has been based on two randomized clinical trials. Palumbo et al randomized patients treated with thalidomide to daily 100mg aspirin, 1.25mg warfarin, or 40mg enoxaparin; they reported a statistically insignificant trend towards a lower incidence of serious thrombotic events in the LWMH arm (5.0%) compared to warfarin (8.2%) or aspirin (6.4%).[97] Of further interest, this study also identified several other characteristics that placed thalidomide treated patients at higher risk for DVTs: age >60, multiple comorbidities, poorer performance status, and patients not treated with bortezomib. Similarly, Larocca's group randomized patients undergoing treatment with lenolidomide to either aspirin or low dose enoxaparin; again, there was a statistically insignificant trend towards lower incidence of VTE in the LMWH group (1.2%) compared to the aspirin group (2.7%).[98] The choice of prophylactic therapy is based on the expected risk of VTE which is dependent on the anti-myeloma therapy used and patient characteristics. Although aspirin is more appealing as an oral agent, LMWH is more effective in situations where the thrombosis risk is high such as in patient treated with the immunomodulatory agents thalidomide or lenalidomide as well as in patients who have additional risk factors for VTE. Most VTEs in myeloma patients occur within the first 6 months after initiation of therapy. [6696] Although prophylactic therapy is usually provided for at least this duration of time, longer periods of therapy may be considered based on therapy- or patient-related risks factors. [99]

In sharp contrast to the association of increased VTE risk with most anti-myeloma therapies, treatment of MM with proteasome inhibitor bortezomib is associated with a significantly decreased risk for VTEs. Importantly, this thromboprotective benefit holds true even when bortezomib is combined with anti-myeloma agents that are usually associated prothrombotic outcomes such a thalidomide or lenalidomide. [100101] The molecular mechanism involved in orchestrating this thromboprotective effect is dependent of modulation of trascription factor Kruppel-like factor 2 (KLF2). As elucidated by Nayak et al, bortezomib therapy is associated with a prolonged time to thrombosis in a mouse model that is dependent upon transcription factor KLF2, a zinc-finger transcription factor with known vasculoprotective benefits. [102]

Conclusion

Cancer patients undergoing systemic treatment for their malignancy are among the highest risk populations for thromboembolic complications; often, the treatment itself contributes to this risk. Recognition of the antineoplastic agents most likely to cause thrombosis can help raise provider awareness and lead to earlier diagnosis and treatment. Studies completed to date do not identify a definitive role for routine thromboprophylactic therapy to all patients

with a diagnosis of malignancy who are undergoing therapy. Current recommendations however suggest that antithrombotic treatment be strongly considered in patients with an especially high risk of VTE based on the diagnosis, therapy, and other patient-related VTE-risk factors.

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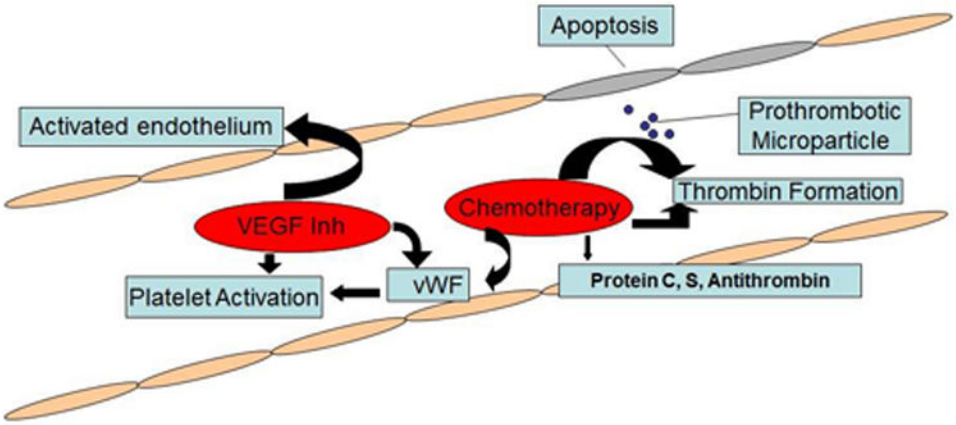

Figure 1.

Cytotoxic chemotherapy has a multifactorial contribution to the risk of thrombosis. It induces vascular injury through apoptosis. In the case of cisplatin, this leads to release of prothrombotic particles that trigger thrombin generation via tissue factor independent mechanisms along with drastically increased vWF activity. Other agents, like 5-FU, also drive thrombin formation in combination with depleted protein C activity. L-asparaginase administration is tied to drastically decreased protein C, protein S, and antithrombin levels, creating a prothrombotic milieu through loss of anticoagulant factors. VEGF inhibition does not directly lead to thrombosis, but instead ‘primes’ the endothelium through a VEGF starved state to be more susceptible to injury. Additionally, platelet activation through PAR-1 and increased Gp llb/llla activity in the case of immunomodulatory agents or increased vWF among others in the case of small molecule inhibitors contributes to this ‘primed’ state.