Thrombosis and Bleeding in Cancer Patients

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Introduction

The writings of Virchow in 1856 were the first descriptions on the way to the understanding of the pathogenesis of thrombosis [1]. Hypercoagulability is a frequent phenomenon in cancer patients. Published knowledge dates back to Armand Trousseau, who described a tendency to "spontaneous coagulation" in two patients with phlegmasia alba dolens and gastric cancer [2]. Since these observations, much progress has been made; it has become clear that activation of blood coagulation not only is a result of the presence of malignant cells; rather, it makes part of the malignant process [3]. Recent years have shown that the pathophysiology is likely to be different in different types of cancer [3, 4]; for example, specific genetic alterations associated with increased thrombogenicity in myeloproliferative diseases, different from solid tumors, have been identified [5]. In general, however, cancer patients display a procoagulant phenotype [6]. But cancer patients are also prone to bleeding due to the properties of the tumor, during interventions or when a disseminated intravascular coagulation [DIC] occurs [7, 8]. This chapter will review the important issues of thrombosis and bleeding in cancer patients from a practical point of view.

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Epidemiology of Hypercoagulability in Cancer Patients

There is ample evidence that cancer patients frequently show increased biochemical markers of plasmatic and platelet coagulation activation (increased prothrombin fragment 1 + 2 and thrombin-antithrombin complex), generation of soluble fibrin (increased fibrinopeptide A and B), fibrin generation and degradation (increased fibrin degradation products, D-dimer), and surrogates of continued platelet activation [9–11]. Such markers of overall coagulation activation prove the procoagulant phenotype [12, 13] in cancer patients. Besides, some of these markers such as fibrin monomer or D-dimer have been shown to be associated with tumor spread [14] as well as progression, response to therapy, and survival [15–17]. In addition, certain genotypes of coagulation proteins seem associated with survival and response to therapy (e.g., PAI-1 in testicular cancer [18] and TFPI in breast cancer [19]), although this is, for now, not part of a management algorithm.

Depending on the type of cancer and the state of the disease, increased surrogate markers of

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coagulation activation can be found in up to 90% of patients. However, one has to recognize that coagulation proteins and markers of coagulation activation make part of a dynamic phenomenon: even largely increased markers of coagulation activation are not predictive of the occurrence of a thromboembolic event in the single patient, although the relative risk is increasing with increasing activation marker concentrations [10, 16, 20–22]. On the other hand, it is well documented that cancer patients have a high prevalence of clinically silent thrombi, as shown by the fact that cancer patients have a high prevalence of thrombi that are detected at autopsy only [23–25].

Venous thromboembolism (VTE) that is cancer associated can precede cancer diagnosis. The highest risks for VTE before a cancer diagnosis is made are found in acute myelogenous leukemia (AML), non-Hodgkin lymphoma (NHL), and renal, ovarian, and pancreatic cancer (approximately three- to fourfold increased risk); the overall risk in cancer patients to develop a VTE as a sign of (the still undetected) cancer is approximately 1.3 [26]. In the first 2 years after a VTE diagnosis is made, the greatest risks for being diagnosed with cancer are found for lymphoma (approximately fivefold) and ovarian cancer (approximately sevenfold) [27]. Prospective studies have also confirmed the association between overt malignancy and VTE. A prospective case-control study of 3220 patients with VTE revealed an overall sevenfold increased risk in patients with cancers. Hematologic malignancies had the highest risk (OR 28), whereas solid tumors had ORs from 2 to >20 [28]. Comparable results for VTE in lymphoma, leukemia, and plasma cell dyscrasias were described in other studies [29]. Besides, various additional comorbidities, including various forms of cancer, are associated with an increased risk of dying in patients admitted to the hospital for VTE [30].

The tumor itself is able to induce (mainly) procoagulant changes, but such changes are also found in relationship to cancer treatment. In a US study, 8% of 66,000 (neutropenic) cancer patients hospitalized were found to develop thromboembolic events (5% venous, 15% arterial events during first hospital admission) [31]. The highest incidence for VTE was found in leukemias and lymphomas and pancreatic, brain, endometrial, or cervical cancer; on the other hand, arterial thrombosis was most commonly seen in hematological malignancies and prostate, lung, and bladder cancer [32]. Immunomodulatory therapy in multiple myeloma is associated with an increased risk for VTE [33]. These observations are well in line with those in other patient cohorts of chemotherapy in solid cancer with an incidence of VTE of 7% within 3 months after chemotherapy and an annual incidence of 11% [34].

Besides its overall predictive properties in hospitalized patients [30], VTE is a significant predictor of a 2-year mortality in breast cancer patients with the greatest effect in patients with local- or regional-stage (hazard ratio 3.5–5) breast cancer [35]. These and similar observations [26] suggest that survival is worse the closer VTE and cancer diagnosis come together. This might be due to a more advanced cancer stage in such situations.

Pathogenesis of Thromboembolism in Cancer Patients

According to Virchow, the main reasons for the occurrence of a thrombosis are changes in blood flow, vessel integrity, and composition of the blood [1]. Aberrant blood flow is frequently observed in situations associated with hyperviscosity, which can derive from both fluid and cellular blood components. As perfusion problems due to hyperviscosity frequently occur in small vessels first, it is easy to understand from a mechanistic point of view that the brain, the heart, the lungs, and the kidneys are frequently affected, with the resulting clinical manifestations [36]. Laboratory tests for hyperviscosity are infrequently performed. Therefore, the recognition of hyperviscosity usually depends on clinical suspicion and supporting laboratory data, e.g., increased monoclonal proteins in multiple myeloma [37]. These can affect flow characteristics via several mechanisms [38]; as hyperviscosity is also a function of the size of the molecules

involved, it is most common with IgM paraproteins [39]. Other (rare) reasons for hyperviscosity can be light chain disease as well as cryofibrinogenemia and cryoglobulinemia [40]. Fibrinogen, which significantly influences blood viscosity and is frequently increased in cancer patients [41], is, as are other hemostatic markers, dependent on the course of the malignant disease [16].

Further important reasons for hyperviscosity are massively increased cell counts [42]. A high hematocrit can convey hyperviscosity, as can be deduced from the thromboembolic risk that is well documented for polycythemia vera (P. vera) patients; thromboembolism is the most frequent cause of death in P. vera [43]. Other factors seem to play important roles, too, such as platelet activation (increased thromboxane formation) [44]) and JAK-2 mutations, shown to be involved in the development of myeloproliferative diseases; specifically, the incidence of thromboembolism seems to depend on the number of alleles affected, but the exact mechanism remains to be elucidated [4, 45–47].

Leukostasis can occur within the microcirculation of the central nervous and respiratory system when hyperleukocytosis is present. It can occur in chronic leukemias, especially chronic myeloid leukemia, but it is rather seen in AML variants with increased blast adhesiveness [48]. Leukostasis is much less frequently seen in lymphoid leukemias: lymphocytes are smaller and seem to have a lower adherence to vasculature, specifically in chronic lymphocytic leukemia (CLL) [49]. Different from myeloid leukemias, leukostasis in lymphoid leukemia might need additional risk factors such as a concurrent infection to upregulate adhesive cell surface molecules in order to precipitate clinical symptoms.

Thrombocytosis is associated with an increased risk for VTE in cancer patients as well: patients with a platelet count of >350 G/l have a significantly increased risk [50, 51]. Also, there is evidence that physical properties such as mean platelet volume (MPV) [52] as well as the degree of platelet activation [21] are associated with the risk for thrombosis in cancer patients.

As most solid tumors or affected lymph nodes grow expansively at some point in time, vessel compression is a further potential reason for the occurrence of VTE in cancer patients. However, the classical example for this situation, the superior vena cava syndrome (SVCS), is probably much rarer than perceived. In a large retrospective cohort of more than 34,000 patients, only 6 had SVCS thrombosis and most had to be attributed to central lines [53]. Any vein might be subject to external compression, thus a reason for VTE [54]. Cancer patients are often immobilized or have to undergo surgery; both situations result in impairment of regular circulation, inducing an additional risk factor (besides the cancer itself). That this risk is severe can be deduced from a prospective cohort in which up to 50% of the deaths early after cancer surgery were due to VTE [55].

As mentioned, direct tumor-associated vessel impairment increases the risk for VTE. Besides outside vessel compression, direct tumor cell invasion of the vessel wall might result in increased risk for VTE; also, the tumor induces tissue factor (TF)-dependent angiogenesis, thereby increasing the exposition of the blood volume to tumor-derived procoagulants [56]. The tumor itself might present as an intravascular mass that induces additional adjacent accumulation of blood cells and fibrin. Emboli directly deriving from tumors are rare but do occur, most frequently in gastrointestinal cancers [57]. This phenomenon might, for example, explain the reduced survival in hepatocellular carcinoma with portal vein tumor thrombi (3-year survival 20% with vs. 56% without [58]), with the extent of the portal vein thrombus likely also being important [59]. Other tumor entities have been found to show similar phenomena.

It is well known that the procoagulant phenotype in cancer is at least partially related to cytokine trafficking from cancer cells, endothelial cells, and peripheral blood cells [60, 61]. This can lead to tissue factor (TF) (over-) expression (e.g., on monocytes), upregulation of procoagulants, downregulation of anticoagulants, platelet activation [62], or neovascularization through proangiogenic signaling [63]. Neutrophils can activate platelets via cathepsins, can produce elastase to degrade the endothelium, can expose

thrombogenic subendothelium [64], and can bind to platelets via various mechanisms [65]. It was recently shown that generation of neutrophil extracellular traps (NETs) in malignancy links the neutrophils to the generation of a prothrombotic state [66], while neutrophilia is associated with an increased risk of VTE in cancer patients with chemotherapy [67].

Tumor cells produce several factors that induce the prothrombotic state in cancer. TF is increased in cancer patients [68] with DVT [69], especially in leukemia and lymphoma [70]. On the other hand, increased profibrinolytic activity might also be encountered in leukemia patients [71] as well as patients with solid tumors [8].

PAI-1 levels are frequently increased in cancer patients, which is associated with an increased risk for VTE in both cancer and non-cancer patients [72]. Whether the 4G/4G polymorphism has direct or indirect (through VTE) influence on the outcome remains to be elucidated [18].

Apoptosis of (tumor) cells results in a prothrombotic state as observed with different malignant and benign cell lines; thrombin generation seems to parallel the degree of apoptosis [73], resulting in increased prothrombotic risk. This offers a mechanistic explanation for the hypercoagulablity observed in tumor lysis syndrome as well as the increased risk of VTE during tumor therapy [74].

Very small membrane fragments are known as microparticles (MP); they derive from normal cells (platelets, blood cells, or endothelial cells) but can also be derived from malignant cells. Microparticles carry TF and may—through the provision of phospholipids—be involved in facilitation of complex formation and thus increased thrombin generation. Recent clinical studies have shown MP to be increased in cancer patients with different tumors [74, 75]. Procoagulant microparticles devoid of TF activity have also been described ([76] see also below).

Cancer patients can acquire a resistance against activated protein C (APC resistance) [29, 77–80], but the exact contribution of this potentially prothrombotic mechanism to the VTE phenotype is difficult to define, given the other prothrombotic mechanisms present in cancer patients.

The antiphospholipid syndrome (APS) is characterized by thromboembolism and the presence of antiphospholipid antibodies (APA, by definition against cardiolipin or β-2 glycoprotein I or a lupus anticogulant; to fulfill the diagnostic criteria for APS, the antibodies have to be found in two separate investigations at least 12 weeks apart). In lymphoma patients, APA seems not infrequent (up to 27%, with an annual rate of thrombosis of 5.1% in patients with APA and 0.75% in those without [81]), well in line with other findings [82]. As in non-cancer patients, the presence of antiphospholipid antibodies in cancer patients seems to be associated with an increased risk of thromboembolism [83, 84]. Although overall causality of the malignant process for the presence of APA seems unlikely [85, 86], some data suggest that antiphospholipid antibody-associated VTE might be the first manifestation of malignancy [84, 87]; whether or not chemotherapy modulates the VTE risk associated with APA is unclear.

Factor V Leiden is the most frequent inherited thrombophilia, also in cancer patients [88]. It confers an approximately 7-fold increased risk for DVT in heterozygotes and an 80-fold increase risk in individuals being homozygous. Overall, its presence seems to add an additional risk factor for VTE in cancer patients besides the cancer itself [89]. The prothrombin 20210A mutation causes increased prothrombin levels and is associated with a relative thrombotic risk of three in heterozygotes. It seems possible, however, that the VTE risk mediated through these most frequent congenital thrombophilias is different in different cancer patient populations [88, 90–92].

Iatrogenic Factors

Chemotherapies and tumor surgery frequently induce a hypercoagulable state [93, 94]. Therefore, cancer patients (and specifically those undergoing chemotherapy) have a high risk of developing thromboembolic events [95]. A special situation is encountered with the use of asparaginase in lymphoproliferative diseases; the initial phase with early reduction in protein synthesis is followed by a phase of hypercoagulability as procoagulants

recover earlier than anticoagulants (mainly antithrombin); this is associated with an increased thrombin generation throughout therapy [96]. Corticosteroids, often used in conjunction, also might increase the prothrombotic risk [97]. Other chemotherapeutic regimens with procoagulant effects include cisplatin, which seems able to induce a TF-independent procoagulant response mediated through generation of (TF free) microparticles from endothelial cells [76]. Thalidomide and analogues such as lenalidomide are also prothrombotic. When used for single-agent therapy in myeloma, less than 2% of patients will develop thromboembolism [98]. In combination with steroids (dexamethasone), however, the rate increases markedly [99] [100]. Cohort studies suggest, however, that prophylaxis with low-molecular-weight heparin (LMWH) can significantly reduce the VTE risk in these patients [101].

Central venous catheters (CVC) are frequently used in order to provide a secure and reliable way for repeated access to the venous system during IV-based therapies. CVCs are believed to be thrombogenic due to the vessel injury to begin with but also because of changes in blood flow as well as provision of an artificial surface in the setting of hypercoagulability from the underlying cancer [102]. Underlying congenital thrombophilia might be an aggravating factor [103], and prevalence might differ with different access sites [104]; prospective data are missing, however. Also, data on the frequency of CVC-related venous thrombosis are not homogeneous [105–108]. In a registry of 2945 cancer patients, deep venous thrombosis (DVT) in the upper extremities overall occured in 6.7%; association with a CVC occured in 3.5% [109]. Other trials suggested ovarian cancer to induce a specific risk for CVC-related DVT [108] and thrombocytopenia to be somewhat protective in this setting.

Management of Hypercoagulable States

As mentioned above, VTE is frequent in cancer patients [6, 110] (with an estimated prevalence of 4–20%) and is the second greatest cause of mortality in cancer. In the past, a prospective randomized clinical landmark trial has clearly demonstrated that long-term use of daily subcutaneous LMWH is more efficient than vitamin K antagonists to prevent recurrent VTE in cancer patients [111], but a recent trial failed to confirm this [112]; a potential explanation for this outcome, besides other things, might be that cancer therapy has considerably changed over the decade that has elapsed between these trials. Various national and international guidelines [113–116] recommend the use of LMWH for 3–6 months for treatment and secondary prophylaxis of VTE in cancer patients. Despite convincing data that effective pharmacological antithrombotic prophylaxis is relevant, many caregivers still seem not to have yet modified their clinical practice [117]. This problem is of significance [118], as there is evidence that up to 40% of patients that developed VTE did not receive the thromboprophylaxis necessary [95, 118]. And this is despite the fact that LMWH long-term use appears well tolerated and may, in some instances, positively influence overall response to therapy [119]. Palliative care patients might be preferring LMWH injections over warfarin or compression stockings, but physicians' preferences also seem to have an important influence on the respective decisions [120–124].

The exact rate of VTE or arterial thromboses [125] with the use of thalidomide and its analogues probably depends on the therapeutic regimens chosen (especially in combination with dexamethasone, see above) and therefore still remains some matter of debate [33, 126], but the frequency of VTE is high enough to suggest that pharmacological thromboprophylaxis, probably preferably with low-molecular-weight heparin, should be used [127, 128].

Pneumatic compression stockings seem to work well for thromboprophylaxis in cancer patients, but randomized controlled studies on their use, specifically in comparison to other pharmacological antithrombotic therapies, are rare [117, 129–131].

At the time being, there is still no unequivocal evidence that antithrombotic prophylaxis will prevent catheter-associated thrombosis in cancer

patients, but available data strongly suggest a rational for the use of antithrombotics [106, 132, 133].

The potential use of direct oral anticoagulants (DOACs, also still referred to as NOAC for "new oral anticoagulants" or "non-VKA oral anticoagulants") in cancer patients is of utmost interest and seems in a transition phase at the time being. The phase III studies for VTE therapy and secondary prophylaxis for dabigatran, rivaroxaban, apixaban, and edoxaban all included patients with VTEs that were later on found to be related to a malignancy. Such patients within these trials (subgroup analyses) as well as "real-world patients" (cohort studies) were separately evaluated; no sign was found that the use of DOACs showed evidence for decreased efficacy or increased toxicity as compared to non-DOAC, standard anticoagulant therapy in the setting of cancer-associated thomboembolism [134–142]. However, as patients with active cancer were excluded from the respective phase III studies, a formal evaluation of the use of DOACs in cancer patients is needed [143]. Such studies are underway. Meanwhile, in VTE found to be cancer associated, our approach is to continue DOACs in patients that were started on it if therapy has been effective and well tolerated. If a malignacy is already known when VTE occurs, we currently still suggest to start therapy with LMWH according to the current guidelines. But as mentioned before, a transition phase is taking place. Should the formal studies confirm the positive initial clinical experience with DOACs in cancer patients, these substances will be an important addition to the current selection of antithrombotic therapies in patients with cancer. Specifically, these substances will likely reduce the need for the subcutaneous application of antithrombotics in many, if not most, cancer patients and thus also increase their quality of life.

Despite being frequently used, aspirin cannot be generally considered as an adequate prophylaxis for primary or secondary prophylaxis of venous thromboembolism in cancer patients [144]. However, in situations where plasmatic antithrombotics are contraindicated and aspirin is not, its use might be considered rather than completely withholding antithrombotic therapy [115].

In hypercoagulable states due to acquired anticoagulant deficiency such as antithrombin deficiency with asparaginase therapy, replacement therapy should be taken into consideration although randomized controlled trials are needed to clarify this question [145, 146].

In patients with hyperviscosity due to paraproteins [37, 80], plasma exchange or plasmapheresis might be the most appropriate way to treat, at least for the short-term benefit. High protein concentrations, however, tend to "rebound" due to the high protein concentrations present in the extravascular space (especially with IgG) [147]. Other reasons for hyperviscosity in cancer patients might exist and thus necessitate different and/or continued therapeutic prophylactic approaches [41]. Recently, this was recognized specifically for JAK-2-positive hematological diseases [148, 149].

Vena cava filters might be an option for the prevention of thromboembolism in patients with manifest thrombosis or very high risk for thromboembolism and bleeding risk with antithrombotic therapy (such as chemotherapy-induced thrombocytopenia) or contraindication to anticoagulation [115], but the consideration itself is a sign of poor prognosis [150]. CVC filters may be associated with device-related thromboembolic complications in nearly 10% of patients [151]; however, in the absence of randomized trials, results from different reports are difficult to compare as survival times of the patients might greatly differ [152]. From a hemostaseological point of view, IVC filters are almost never needed and frequently create more problems than they solve [153].

Pathogenesis of Bleeding

Besides thromboembolic events, cancer patients show also evidence of a bleeding tendency. This can be related to various, seemingly separate pathologies; however, recent research suggests that bleeding might occur, in fact, as the result of an interplay of various different pathologies [154–156].

Thrombocytopenia

Drug-induced thrombocytopenia is a frequent finding in cancer patients undergoing chemotherapy [157]. It is common knowledge that thrombocytopenia increases the risk of bleeding, both in cancer and non-cancer patients [158]. In thrombocytopenic patients, additional risk factors for bleeding are infection, antithrombotic therapy, signs of renal dysfunction, and anemia [159]. In acute leukemia, the degree of thrombocytopenia correlates well with the risk and degree of bleeding. Fever and infection not only increase the bleeding risk but also reduce the response to platelet transfusion [160]. There is some well-based evidence that platelet substitution in AML induction chemotherapy can be lowered to trigger levels of 10 or 20 G/l [161]; the same group performed a randomized clinical trial indicating that a non-prophylactic approach *outside* induction or reinduction therapy for acute leukemia might be reasonable if the staff involved is sufficiently experienced [162].

Although bleeding does occur during treatment for solid cancers such as lung cancer, it seems that thrombocytopenic bleeding in solid cancer patients is rather rare [163]. Defining the exact need for platelet transfusion seems relevant as treating patients in this setting consumes considerable resources, with approximately half of the therapy courses inducing the additional financial burden [164]. It is important to preemptively consider the need for platelet support in advanced cancer patients on a case-by-case basis; this should allow to provide the therapy necessary and, at the same time, to reduce the strain on the resources available [165, 166].

Platelet Dysfunction

The potential reasons for platelet dysfunction are manifold; most frequently, platelet dysfunction is drug induced [167], including anticancer drugs such as tyrosine kinase inhibitors [168]. Unexplained GI bleeding is frequently associated with nonsteroidal anti-inflammatory drugs (NSAIDs) or anticoagulants [169]; NSAIDs impair mucosal healing or directly induce mucosal toxicity, both properties that will increase the risk for bleeding, e.g., in the gastrointestinal tract [170]. In that respect, COX-2 inhibition could be an attractive target in cancer patients with pain [171]; however, as COX-2 inhibitors may be associated with increased cardiovascular risk [172], the decision to use them should be carefully evaluated and be taken on a case-by-case basis.

Tumor Infiltration

Bleeding in cancer patients might be due to direct infiltration of the respective vessel, as it can be encountered, for example, in gastric lymphoma; here, therapy has shifted away from primary surgery. But if bleeding occurs, early surgical intervention needs to be considered [173]. Radiation therapy might be an appropriate approach to control bleeding that comes from direct tumor infiltration [174]; rarely, however, radiotherapy can aggravate or induce bleeding in sensitive tumors, especially when applied in combination with chemotherapy [175].

Fibrinolysis

Many malignancies might be associated with an increased fibrinolytic activity [8, 176]. Along with elevated levels of plasminogen activators in many hematological malignancies, excessive fibrinolysis can increase the risk of bleeding [177]. In DIC (with increased fibrinolysis), the extent of bleeding correlates with fibrinolytic activity [178], as is probably the case in acute promyelocytic leukemia [71]. The increased fibrinolytic response in APL might have to do with the increased expression of uPA [179] and Annexin II [180], a receptor for tPA and plasminogen. Annexin II has been found to be highly expressed in in cerebral endothelial cells [181], which may explain why intracranial hemorrhage in APL seems frequent and provides a rational for the prophylactic use of antifibrinolytics. Annexin II might also contribute to bleeding in other acute leukemias [180]. The

standard use of antifibrinolytics seems helpful to reduce bleeding and thus the use of blood products [182], but requires careful consideration of the concurrent thrombembolic risk.

Rarely, coagulation factor inhibitors are found in cancer patients; in this situation, bleeding complications can be severe [183] (see also "Paraproteins" below).

Perioperative Bleeding Problems in Cancer Patients

Perioperative coagulopathies continue to be a diagnostic and therapeutic dilemma, especially in cancer patients. The pathophysiology behind unexplained intraoperative coagulopathies is of great variety and complexity as all aforementioned mechanisms can occur [154, 184–187]. If the pathophysiology is known, therapy should be directed accordingly. We showed in prospective studies that patients with "unexplained" intraoperative coagulopathy have significantly less factor XIII per unit thrombin available at any point in time [188], resulting in the loss of clot firmness and increased intraoperative blood loss. These patients have less cross-linking capacity to begin with, explaining their preoperatively increased fibrin monomer concentration, which can be used for preemptive risk stratification [189]. Importantly, the relative (compared to the amount of thrombin generated) acquired FXIII deficiency shows clinical relevance with surgical stress even if deficiency is moderate, which differs from the experiences in patients with inborn FXIII deficiency. There is proof of principle that the use of FXIII in high-risk patients (high preoperative fibrin monomer) leads to maintenance (vs. loss) of clot firmness and significant reduction in blood loss [190].

Adverse Effects of Therapies

Drugs used for oncologic therapies frequently induce myelosuppression, which can cause thrombocytopenia and thus induce bleeding [191]. In addition, other mechanisms might include direct or indirect influences on platelets (such as tyrosine kinase inhibition [168], see above) and coagulation factors: L-asparaginase, used for the treatment of acute lymphocytic leukemia, induces a depletion in L-asparagine, leading to an impaired protein synthesis that also extends to procoagulants, anticoagulants, and fibrinolytic proteins. The lowering of various procoagulants induces a transient hypocoagulable state that is at least partially balanced due to the parallel decrease of anticoagulants [96, 192]; however, replacement of coagulation factors in high-risk situations might be appropriate and needs to be decided on a case-by-case basis.

Paraproteins

High levels of paraproteins can interfere with hemostasis in various ways: they can inhibit polymerization of fibrin monomers, interfere with platelet aggregation, or inhibit clotting factor activity [193, 194]. As already described for hyperviscosity, bleeding problems in such patients might improve with plasmapheresis (but also might rebound with redistribution). Although this can be a clinically important in single patients, it is a rare problem.

Conclusions

Hypercoagulability in cancer patients not only is an attendant phenomenon but in fact is part of the problem. Therefore, the stringent evaluation of the need for thromboprophylaxis or continued use of anticoagulant therapy in every cancer patient is a must, especially as recent data suggest that the use of low-molecular-weight heparin might improve clinical outcome, whereas at the same time, not all patients in need of thromboprophylaxis will receive it.

On the other hand, our knowledge of the use of blood products in cancer patients has evolved (e.g., platelet transfusion in leukemia patients) and should thus allow us to make better use of the available resources, avoiding unnecessary burden and risk to the patient and economic strain to the healthcare system.

Studies in recent years have advanced our understanding of thromboembolism and bleeding complications in cancer patients. The next important step to come will be to define the adequate use of direct (or "novel") oral anticoagulants in cancer patients. Other issues such as specific problems and therapies with disease-specific approaches (e.g., JAK-2-positive diseases) are on the horizon, indicating that we will need to continue prospective controlled trials to generate further evidence-based knowledge.

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