Malignancy and Hemostasis

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Abstract

The presence of cancer may predispose the patient to a hypercoagulable state. Approximately 15% of all patients with a malignancy may be affected by some form of thromboembolic disease. Trousseau's syndrome relates to this predisposition to both arterial and venous coagulation in this cohort of patients. This well-documented state affects the local tumor site as well as causes these systemic effects. The additional burden on the patient of potential immobility, chemotherapy, surgery, indwelling lines, and nutritional deficit make thromboembolic disease more prevalent. It must also be borne in mind that malignant disease may also result in a greater bleeding tendency due to dysfunction with components of the coagulation cascade. Additionally, many patients may be on anticoagulant therapy, and bone marrow disorders such as leukemia may cause thrombo-hemorrhagic complications.

The oral surgical management of cancer patients in regard to hemostasis is a complex interplay of history, physical findings, laboratory values, and provider preference. There is limited high-quality information available regarding the specific oral surgery population, and therefore the best recommendations are extrapolated from available studies and guidelines in the medical and surgical literature. The ultimate decision is at the discretion of the treating provider to ensure procedures are executed appropriately, and there is a plan for monitoring in the postoperative period. Certainly the patient and treatment factors which place patients at greater risk for bleeding should be evaluated together in consultation with the patient's oncologist prior to surgery. Once the risk of bleeding is established, laboratory testing guides consideration of preoperative transfusion, further medical management, or alteration of the surgical plan to reduce risk of bleeding intraoperatively. Scheduling surgery to accommodate for the expected bone marrow recovery following the drop in the patient's blood counts is also a helpful measure. Reducing the extent of

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surgery and dividing treatment into multiple visits can decrease the stress on the patient's hemostatic mechanisms. Careful attention to surgical technique to minimize tissue trauma and blood loss is essential, and local hemostatic measures discussed elsewhere are helpful adjuncts.

7.1 Introduction

The presence of cancer may predispose the patient to a hypercoagulable state. Approximately 15% of all patients with a malignancy may be affected by some form of thromboembolic disease [1]. Trousseau's syndrome relates to this predisposition to both arterial and venous coagulation in this cohort of patients [2]. This well documented state affects the local tumor site as well as causing these systemic effects [3]. The additional burden on the patient of potential immobility, chemotherapy, surgery, indwelling lines, and nutritional deficit make thromboembolic disease more prevalent [4]. It must also be borne in mind that malignant disease may also result in a greater bleeding tendency due to dysfunction with components of the coagulation cascade. Additionally, many patients may be on anticoagulant therapy, and bone marrow disorders such as leukemia may cause thrombo-hemorrhagic complications [5].

This chapter seeks to cover all aspects of acquired coagulation disorders related to malignancy and how these may impact on the management of oral disease. The aim is to gain an appreciation of the cancer patient presenting with a tendency toward clotting or hemorrhage and thus have an algorithm in mind for their dental treatment so as to minimize potential complications that may arise.

7.2 Hypercoagulability

Thromboembolic manifestations are the most frequent complication of patients with a malignancy [6]. These are most commonly venous thromboembolism (VTE) in the form of either deep vein thrombosis or pulmonary embolism [7]. Malignancy will have effects on all features of Virchow's triad [8]. It is known that abnormalities in the hematological clotting screen may be abnormal with malignancy even if there is no evidence of clinical manifestations [9]. A solid-state tumor has the ability to leak fibrin into the local environment and also has effects systemically. This along with fibrinolysis is more predominant in patients with metastatic disease thereby increasing the preponderance for hypercoagulability [10].

Recently interesting developments have shown a strong correlation between platelets and cancer-related thrombosis [11]. A subset of platelets called COAT (collagen and thrombin) have a high level of factor V bound to the surface and are related to thromboembolic events [12, 13]. High factor VIII levels and low protein C levels also had a predictive value for thrombosis in patients with malignancy [14].

7.3 Tumor Effects

The presence of a tumor may have several local effects, as procoagulant molecules are evident of the surface of cancer cells [15]. In addition, as the tumor shed cells, this initiates a blood-borne phase of the clotting cascade. These metastatic cells encourage thrombus formation surrounding them containing both fibrin and platelets [16, 17]. It was originally postulated that for tumors to spread via a hematogenous route, then activation of the coagulation cascade was necessary [18]. This has subsequently been proven in animal models to be the case [16, 17].

Tissue factor (TF) seems to play a central role in tumor-related coagulation [7]. TF is needed for activation of clotting factors in plasma. It forms a complex with factors VII and VIIa that then initiate the coagulation protease cascade [19]. TF expression is increased not only by cancer cells but also by the tissue surrounding the tumor [20, 21]. The subsequent thromboembolic events caused then result in hypoxia and the expression of vascular endothelial growth factor (VEGF) resulting in angiogenesis and cancer growth [22].

There is a measurable aspect to this as shown by a study that demonstrated increased venous thromboembolism in patients with high tumor expression of TF [23]. In mouse models that focused specifically on colorectal cancers, activation of the oncogene, k-ras, and inactivation of the tumor suppressor protein, p53, caused increased TF expression [24]. Many studies show that TF is critical to overall survival. Its expression is related to increased angiogenesis, poorer histological differentiation, and a higher rate of blood-borne metastasis leading to a less favorable outcome. The processes by which TF causes tumor progression have been proposed by Langer and Bokemeyer to be either coagulation-dependent or coagulation-independent mechanisms [7]. With regard to the mechanisms that are dependent, the production of thrombin with the subsequent conversion of fibrinogen to fibrin causes the activation of platelets and the formations of an extracellular matrix that leads to tumorigenesis. The independent mechanism functions via TF and factor IIa complexes signaled through protease-activated receptors. This process causes enhanced cell proliferation with invasion and angiogenesis that is associated with tumor progression and decreased survival. It is the TF in the cytoplasm that purportedly causes the upregulation of VEGF and subsequent angiogenesis [25]. The current thinking is that TF present in the bloodstream is more likely to be the cause of VTE in cancer patients than TF produced from the primary tumor. It is via this pathway that it can have a direct effect on hypercoagulability. A retrospective analysis showed that the incidence of VTE was 35% in patients who demonstrated TF-positive microparticles as opposed to 0% without evidence of these microparticles [26]. These microparticles are usually introduced into the circulation directly from the cancer cells and can thus exert their effect. Correlation has been demonstrated between levels of these TF-related microparticles and D-dimer that has emerged once again as a valuable measure of coagulability [27]. Several other studies have demonstrated that the surgical removal in patients who had localized tumors resulted in a corresponding rapid decrease in the TF-related microparticles [7]. The mechanism by which TF promotes metastases is also linked closely with it promotion of hemostasis. With regard to lung metastases, it has been directly proven that the formation of a fibrin-platelet clot around tumor cells enables both spreading and protection from natural killer cell-mediated cytotoxicity [28]. In mouse models disruption of this TF-initiated cascade effectively suppressed lung metastases [29]. However, this has not been demonstrated effectively in clinical models due to concerns regarding the risks of bleeding associated with anti-TF treatment. Outside of lung metastasis, the inhibition of Trousseau's syndrome by blocking TF has been investigated in experimental and preclinical studies by either the downregulation of TF or the destruction of TF-expressing tumor cells. Overall, the TF-related link between hypercoagulability and cancer spread has also not been convincingly proven, and further work is currently ongoing. Several other molecules have also been described to have a procoagulant effect in malignancy.

Cancer procoagulant, fibrinolytic molecules and cytokines (e.g., TNF-α and IL-1β) that are released by tumor cells have also been shown to have thrombotic effects [30].

The proinflammatory cytokine tumor necrosis factor alpha orchestrates complex multicellular processes through a wide variety of changes that it induces in cell functions. TNF-alpha is produced by tumor cells constitutively and in turn induces the expression of tissue factor by the vascular endothelial cells [31, 32].

Cancer procoagulant (CP) is another such procoagulant. CP is a cysteine protease which is a substrate for factor X in the coagulation cascade. CP can activate factor X independently and cleaves its heavy chain site at a different location compared to other known factor X activators [30, 33, 34]. CP has been detected in several extracts of tumor cells [30, 35, 36]. CP has been shown to be elevated up to 85% of cancer patients [30, 37].

Platelets also play a major role in the tumor microenvironment. They play a crucial role in promoting tumor growth and metastasis. In solid tumors, many studies have shown that platelets play a major role in protecting tumor cells from

natural killer (NK) cell-mediated lysis [38, 39]. Furthermore, platelet-coated tumor cells were physically shielded from lysis by NK cells, and this protection is not a result of passive agglutination but required platelet activation. Upon aggregation by tumor cells or physiological factors, platelets mobilize to their surface membrane glucocorticoid-induced TNF-related ligand (GITRL). This leads to the platelet-coated tumor cell are protected, from NK lytic activity and also interferon-gamma secretion due to the interaction of the GITRL interaction with its receptor GITR on the NK cells. Soluble factors are also secreted by these platelets which inhibit NK antitumor activity. Therefore, platelets not only protect tumor cells from NK-mediated lysis within the circulation but also potentially within the tumor microenvironment via signaling by secreting soluble factors [40, 41].

In hematological malignancies, platelets on the contrary are inhibited from aggregation. Platelets derived from acute and chronic myeloid leukemia (AML and CML) patients tend to have impaired platelet responsiveness to physiological responses. In addition, they may have platelet storage deficiency and, commonly in AML, disease- and treatment-induced thrombocytopenia [42–45].

Tumors may have an additional physical effect causing thrombosis by disturbing bloodflow. This can be via direct pressure causing alteration in flow or injury to the intima of the vessels [1]. This is particularly notable in renal cell carcinoma that is strongly associated with inferior vena cava thrombosis [46]. This has been shown to be the case in 4–10% of renal tumors [47].

7.4 Chemotherapy

The treatment of malignant disease with chemotherapy is associated with an increase in the risk of developing VTE by up to six times that of the control group [48, 49]. Most patients who develop VTE do so in the outpatient setting [50]. A significant amount of research was done in the field of breast cancer, and it was shown that both tamoxifen and chemotherapy increased the risk of VTE [51, 52]. Cisplatin-based chemotherapy demonstrated the prevalence of VTE to be 17% compared to 7% for any chemotherapy [53, 54]. It is postulated that this is independently related to endothelial injury, hypomagnesemia, and raised levels of von Willebrand factor [55, 56]. Overall, the acknowledgment is that the polypharmacy of chemotherapy can increase the risk of VTE. The use of anticoagulants, to reduce thromboembolic events in patients undergoing chemotherapy for malignancy, will also impact on the management by the dentist. This will be discussed later in this chapter.

7.5 Medical Devices

The management of patients with malignancy, particularly those undergoing chemotherapy, will usually necessitate the placement of a central venous catheter (CVC). This will facilitate the administration of drugs and sampling blood for hematology and chemistry. It is acknowledged that the presence of this device will increase the risk of DVT particularly in the upper limb on the same side and also consequently PE [57]. The injury to the vessel wall that occurs upon its placement may contribute to an increased rate of thrombotic event [58]. This has been documented to occur in 2/3 of patients with cancer. Catheters placed in the left subclavian vein appear to have an increased risk compared to those on the right [59]. Several other variables exist that can affect the development of a DVT related to CVCs including the material used to construct the catheter and the fluid infused through it. The use of total parenteral nutrition is more likely to cause a DVT than a crystalloid solution [60]. It has also been proposed that increasing the number of lumens of the CVC may increase DVT rates. Finally, catheters that contain the use of polyvinyl chloride are more thrombogenic than those containing polyurethane [61].

7.6 Surgery

The management of oncology patients for outpatient dental or oral surgical procedures begins with a multifactorial medical and dental assessment. The proposed procedure and its complexity

should be considered in relation to the patient's overall health status and expected prognosis in consultation with the patient's oncologist. With modern advances in cancer treatment, patients are often managed with chronic chemotherapy or immunotherapy even in the face of metastatic disease and have a much longer life expectancy than in the past. Dental providers are therefore tasked with managing this new subset of complex patients.

Oncology patients require careful attention to the history and physical examination in preparation for invasive procedures. Important features of the history should be identification of the type of cancer, its stage, the proposed or current treatment regimen, and current medications. Treatment approaches may include a combination of surgery, radiotherapy, chemotherapy, or immunotherapy. The management may also differ based on prognosis and whether the intent is curative or palliative therapy. Knowledge of the care provided is essential in determining the duration and magnitude of impact on hemostasis, immune response, and wound healing prior to undergoing surgical procedures.

The medical treatment of cancer often results in hemodynamic changes which place the patient at increased risk of intraoperative or postoperative hemorrhage, and this is a key component to assessing the patient's candidacy for surgery. Consultation with the patient's oncologist will provide additional details and provide the dental provider a risk assessment regarding the care of patient. In general, the most ideal approach is to provide dental examinations and management of dental pathology prior to initiation of radiation or oncologic treatment. In the event that this is not the case, the dentist must be prepared to be involved in treatment of patients with pre-existing cancer diagnoses and ongoing treatment.

Medical history taking is the most important component of evaluating hemostatic function [62]. At the consultation appointment, all patients should be questioned regarding any pre-existing bleeding disorders, easy or frequent bruising, prolonged bleeding with minor trauma or prior surgery, or episodes of spontaneous bleeding. Melena or hematochezia, hematuria, menorrhagia, epistaxis, and bleeding from mucous membranes are signs of derangement of hemostasis. Examination of the patient should not only be focused on the oral cavity but on the patient as a whole. Evidence of prior bleeding may be seen on a routine physical examination and include petechiae, ecchymosis, or hematomas. Pallor of the conjunctiva and cutaneous ecchymosis may indicate significant anemia. Jaundice, icteric sclera, and abdominal fullness could signify liver dysfunction related to chemotherapy toxicity or previous disease. While a full physical examination is not the responsibility of the dentist, careful attention may prompt further investigation by history or laboratory studies.

Hemostatic derangements are commonly found on laboratory testing in cancer patients, related to severity of disease and duration of both illness and treatment. One study of 40 patients with solid tumors found 80% had two or more abnormal hemostatic tests; another showed an even higher proportion at 92% [63]. A significant portion of the patients had elevated D-dimer levels, which signified a hypercoagulable state, as previously discussed. However, thrombocytopenia was noted in 12.5% and coagulopathy signified by prolonged PT/PTT in 40%, indicating risk of bleeding. Along with the prolonged PT/PTT, there was also a significant difference between the normal control group's platelet count and the cancer patients [64]. Both of these findings are indicative of the abnormal hemostasis and supportive of the need for laboratory studies in patients with known malignancy.

The presurgical laboratory workup of patients with malignancy focuses on the hematological and immune system abnormalities commonly seen either as a result of treatment or from the cancer itself. Cancer infiltration of the bone marrow may be seen in primary lesions such as lymphoma or from metastatic spread from virtually all cancers. Breast, prostate, and lung are the most common cancers associated with bone marrow invasion [65]. Once the bone marrow is 80% saturated with cancer cells, the production of myeloid and lymphoid cell lines are significantly inhibited, leading to reduction in circulating red blood cells (anemia), platelets (thrombocytopenia), and white blood cells (leukopenia) [66]. Bone marrow suppression is also a common side

effect of many chemotherapeutic drugs and results in similar cytopenias. Radiation may induce some bone marrow suppression by encompassing those sites during treatment; however, it is less commonly seen than with patients receiving chemotherapy [67]. Platelet function abnormalities have also been reported with malignancy, due to the myeloproliferative process, but these are challenging to diagnose. Bleeding time testing is notoriously unreliable and it has limited usefulness [68]. A platelet function test is expensive and seldom warranted as a baseline evaluation. A key factor in evaluating these patients is the timing of any previous chemotherapy or planned cycles. The effect of treatment on the bone marrow is a cyclic process which follows a generally predictable pattern in which the platelet count begins to fall approximately day 7 following treatment, reaches the low-point at day 14, and returns back to baseline levels between days 28 and 35 [69].

As indicated above, cancer patients are more likely to have a coexisting coagulopathy in addition to the myelosuppressive effects of chemotherapy and radiation. The causes are varied. Malnutrition can lead to vitamin K deficiency and therefore inadequate production of active coagulation factors [70]. Hepatotoxicity of chemotherapeutic drugs (methotrexate, fludarabine, azacytidine) can cause abnormal hepatic synthetic function of clotting factors, although the effects are usually transient [71]. Disseminated intravascular coagulation (DIC) may be found in approximately 7% of cancer patients, with either the hypercoagulable form (clotting) or the hypocoagulable form which induces bleeding from lysis of fibrin clots. Circulating heparin-like anticoagulants are produced in occasional patients afflicted with multiple myeloma [72]. Coagulopathy can be identified by elevated prothrombin time (PT) and standardized INR results as well as prolonged partial thromboplastin time (PTT). In general, the INR should be within the range of 2–3 for elective dental procedures in an outpatient setting. Patients with coexisting coagulopathy, thrombocytopenia, or anemia are a challenge even for the most routine of oral surgeries. These patients may benefit from a hospital setting where easy access to blood products is available in the case of significant bleeding. Vitamin K or fresh frozen plasma may sometimes be required to transfuse active clotting factors to correct hemorrhage in patients with underlying coagulopathy [73].

Thrombocytopenia is usually identified on a complete blood count by reduction in the platelet count below the normal level of 150,000–400,000. The causes are generally decreased production by myelosuppression, increased destruction by drug-related effects, and sequestration by splenomegaly. Chemotherapy causes approximately 2/3 of all thrombocytopenia in cancer patients [74]. Values below 100,000 often require reduction in chemotherapy dosing [75]. Severe platelet deficiency of less than 50,000 occurs in 20–25% of those receiving chemotherapy, according to 2 major studies of 4956 patients [76, 77]. Despite this high frequency of significant thrombocytopenia, spontaneous bleeding is a less frequent complication, occurring in only 9% of treatment cycles [78]. The highest risk has long been thought to occur when platelet counts drop below 20,000, which was established in the 1960s in a study of patients with acute leukemia [79]. This has been the standard threshold for platelet transfusion in patients who are otherwise asymptomatic and not undergoing surgical procedures in the hopes of reducing spontaneous hemorrhage [80].

Subsequent authors have challenged the absolute use of the platelet count as the only variable to determine risk. The study by Ducher found 84% of significant bleeding events began when the platelet count was between 20,000 and 50,000, with a population of 1274 patients. This is evidence of significant variability from patient to patient regarding bleeding at specific platelet counts, which is important when considering the threshold for transfusion or the safety of even minor surgery procedures. A more recent study by Friedman found that platelet count was not correlated at all with episodes of bleeding, and the most significant factor was a history of prior bleeding events [81]. A retrospective study by Slichter supports the previous conclusions and found importance not in the platelet count, but in a history of bleeding within 5 days [82]. Another

study indicated a prior history of bleeding, presence of bone marrow metastasis, and highly myelosuppressive chemotherapy were all associated with hemorrhage [83]. Certain chemotherapeutic drugs are known to have higher incidence of myelosuppression. Cisplatin, methotrexate, fluorouracil, vincristine, cyclophosphamide, doxorubicin, and etoposide are medications causing thrombocytopenia severe enough to warrant delay in radiation therapy [84]. Elting in 2002 identified cisplatin, carboplatin, lomustine, carmustine, dacarbazine, and mitomycin C as agents considered extremely toxic to bone marrow which were more associated with bleeding [85]. Many other agents have intermediate risk.

All of these factors in addition to the laboratory values should be considered when assessing oncologic patients and their risk stratification in preparation for oral surgical procedures. The studies cited above all dealt with asymptomatic patients who were not undergoing surgical procedures. The risk of uncontrolled hemorrhage is likely higher during surgery as increased stress is placed on the coagulation process. Current guidelines from the American, British, and Canadian systems for surgery (excluding neurosurgery) reflect this concern and consider preoperative transfusion indicated to maintain a platelet count >50,000 [86–88]. Thrombocytopenic patients have been found to be safe for routine dental extractions, in a single study with some limitations. Fillmore in 2013 studied 68 patients with a platelet count under 100,000 and found 7.4% had postoperative hemorrhage, which responded to local measures [89]. The study concluded that neither the transfusions nor hemostatic measures had any outcome on bleeding risk, although the authors indicated the use of local measures remains the judgment of the treating dentist. This study is of limited sample size and did not seek to stratify the results based on severity of thrombocytopenia; therefore the results are of limited value. The authors did seem to reflect the recommendations by others that oral surgical procedures are safe above the 50,000 platelet level. More substantial research is indicated for the safety of oral surgical procedures in this patient population.

Anemia is defined as decreased red blood cell mass, amount of hemoglobin, or volume of RBCs based on standardized numbers set by gender [90]. Normal hemoglobin values are between 12–16 g/dL for women and 14–18 g/dL for men [91]. The World Health Organization classifies anemia as mild (10 mg/dL to the lower limit of normal), moderate (8–9.9 g/dL), severe (6.5–7.9 g/dL), and life-threatening (<6.5 g/dL). While anemia does not cause intraoperative bleeding, significant bleeding may worsen pre-existing anemia, increasing postoperative morbidity, and it is therefore important to note in the operative management of oncology patients. One study identified 63% of patients with cancer diagnosis presented with anemia, which increased with advancing cancer stage [92]. Anemia may result from many different mechanisms in cancer patients. Patients with gastrointestinal lumen cancers or genitourinary cancers may lose blood through direct bleeding from the neoplasm itself. Those with bone marrow invasion or metastasis lack ability to produce active red blood cells. The inflammatory products of cancers (IL-1, IL-6, TNF-α) can also restrict survival of red blood cell precursors, leading to anemia [93]. Hemolysis of existing RBCs may be the result of autoimmune processes or drug related [94]. Malnutrition is a common cofactor in cancer which reduces iron stores and therefore leads to anemia [95]. However, the most common cause of anemia in cancer patients by far is treatment with chemotherapy or radiation, inducing a suppression of red cell production.

A routine complete blood count includes both hemoglobin and hematocrit values, will promptly identify anemia, and should be included in basic preoperative laboratory testing for these patients as mentioned previously because it will also screen for thrombocytopenia. The management of cancer-associated anemia is complex but in general utilizes iron supplementation, erythropoietic-stimulating agents (ESAs), and blood transfusions [96]. In placebo-controlled trials of ESAs, 2–3 weeks was required before a significant difference was found between the epoetin and placebo groups [97, 98]. Therefore, transfusion is the recommended option when rapid correction of

hemoglobin levels is required [95]. This could be for emergent surgeries or more severe or symptomatic anemia. In general, stable patients with hemoglobin levels of 7–8 do not require red blood cell transfusion unless major bleeding is expected [99]. Patients with mild to moderate anemia are usually able to be managed as outpatient surgeries, while symptomatic or severe anemia may require blood transfusion prior to surgical procedures or warrant completion of those procedures in a hospital setting. Identifying anemia during preoperative evaluation, optimizing hemoglobin levels, and minimizing blood loss during surgery are key components to the management of cancer patients undergoing oral surgery, who often require simultaneous management of thrombocytopenia or anticoagulation.

In summary, the oral surgical management of cancer patients in regard to hemostasis is a complex interplay of history, physical findings, laboratory values, and provider preference. There is limited high-quality information available regarding the specific oral surgery population, and therefore the best recommendations are extrapolated from available studies and guidelines in the medical and surgical literature. The ultimate decision is at the discretion of the treating provider to ensure procedures are executed appropriately, and there is a plan for monitoring in the postoperative period. Certainly the patient and treatment factors which place patients at greater risk for bleeding should be evaluated together in consultation with the patient's oncologist prior to surgery. Once the risk of bleeding is established, laboratory testing guides consideration of preoperative transfusion, further medical management, or alteration of the surgical plan to reduce risk of bleeding intraoperatively. Scheduling surgery to accommodate for the expected bone marrow recovery following the drop in the patient's blood counts is also a helpful measure. Reducing the extent of surgery and dividing treatment into multiple visits can decrease the stress on the patient's hemostatic mechanisms. Careful attention to surgical technique to minimize tissue trauma and blood loss is essential, and local hemostatic measures discussed elsewhere are helpful adjuncts [100].

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