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Management of Bleeding in Patients with Advanced Cancer

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Key Words. Bleeding · Hemorrhaging · Cancer · Palliative

ABSTRACT

Bleeding occurs in up to 10% of patients with advanced cancer. It can present in many different ways. This article provides a qualitative review of treatment options available to manage visible bleeding. Local modalities, such as hemostatic agents and dressings, radiotherapy, endoscopic ligation and coagulation, and transcutaneous arterial embolization, are reviewed in the context of advanced cancer, as are systemic treatments such as vitamin K, vasopressin/desmopressin, octreotide/somatostatin, antifibrinolytic agents (tranexamic acid and aminocaproic acid), and blood products. Considerations at the end of life are described. *The Oncologist* 2004;9:561-570

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. List at least four local hemostatic agents and dressings for controlling localized bleeding in a patient with cancer.
2. List at least four systemic therapies for controlling bleeding in a patient with advanced cancer.
3. Describe a decision-making process related to managing bleeding in an end-of-life cancer patient.

INTRODUCTION

Hemorrhaging occurs in approximately 6%-10% of patients with advanced cancer [1]. When visible, it can be particularly distressing to patients and their caregivers [2, 3]. In some patients, it may be the immediate cause of death. This article focuses on hemorrhaging that is visible, as opposed to occult bleeding. It reviews treatment options in the context of advanced cancer.

Etiology and Clinical Presentation

Bleeding may result from local vessel damage and invasion or from systemic processes such as disseminated intravascular coagulopathy (DIC) or abnormalities in platelet functioning and number. The underlying causes of these abnormalities are varied and include liver failure, medications such as anticoagulants, chemotherapy, radiotherapy, surgery, and the cancer itself [4]. Occasionally, concurrent diseases, such as idiopathic thrombocytopenia, may be responsible. Hemorrhaging may manifest in a variety of ways, including hematemesis, hematochezia, melena, hemoptysis, hematuria, epistaxis, vaginal bleeding, or ulcerated skin lesions [4]. It may also present as ecchymoses, petechiae, or bruising. Hemorrhage may occur as an acute catastrophic event, episodic major bleeds, or ongoing low-volume oozing. These characteristics provide clues as to the underlying cause and guide management.

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MANAGEMENT: GENERAL MEASURES

Treatment needs to be individualized and depends on several factors, including the underlying cause(s), the likelihood of reversing or controlling the underlying etiology, and the burden-to-benefit ratio of the treatment, all in the context of the patient’s overall disease burden, life expectancy, and goals of care. If the patient’s life expectancy and overall quality of life warrants it, then management of an acute bleeding episode consists of general resuscitative measures, such as volume and fluid replacement, and specific measures to stop the bleeding. On the other hand, if the patient’s goals of care are palliative, then management may include measures to stop the bleeding without full resuscitative measures. Comfort measures only may be most appropriate for end-stage patients.

Management should focus on identifying the underlying cause(s) and, where possible, controlling the bleeding. A comprehensive history and examination is self-evident. A review of concurrent medications and other illnesses may be helpful in identifying the etiology or contributing factors, such as the concurrent use of nonsteroidal anti-inflammatory drugs, which may exacerbate or precipitate bleeding through their actions on the gastrointestinal tract and platelet functioning [5]. The burdens and risks of prophylactic anticoagulation may outweigh the benefits in patients with very advanced disease. Even when treated with appropriate therapeutic doses of anticoagulants, the incidence of bleeding complications remains higher in patients with advanced cancer than in those with earlier-stage disease [6]. Investigations may be helpful. Full blood counts and clotting profiles may reveal systemic problems, while angiography or endoscopic studies may identify the site of bleeding. Goals of care should be explored. General measures may include applying pressure over the wound, and protecting the bleeding area from trauma and from the remaining infected granulation tissue [7].

Patients at high risk for bleeding should be identified, and preventative measures should be taken before a crisis occurs. Episodic, low-volume bleeding (e.g., hemoptysis) may herald larger, catastrophic hemorrhages. Caregivers of patients at risk for major bleeds ought to be informed and prepared for such an event. However, this should be done sensitively so as not to invoke too much fear.

MANAGEMENT: LOCAL INTERVENTIONS (Table 1)

Packing, Hemostatic Agents, and Dressings

Packing can be used with or without pressure to achieve hemostasis when bleeding originates in the nose [8, 9], vagina [10, 11], or rectum [12, 13]. Surgical swabs of varying sizes may be used. These can be coated with chemicals that facilitate hemostasis; for example, acetone in vaginal packing [10, 14] and cocaine in nasal packing. If possible, the frequency of dressing changes should be reduced, and nonadherent dressings should be used. Specially designed catheters with inflatable balloons may be used to control severe epistaxis. Foley catheters have also been used for this purpose. Such measures are temporary, since prolonged pressure may cause local ischemia.

A variety of agents and dressings, mostly designed for surgical procedures, has been reported to be of benefit for exterior, topical use in patients with advanced cancer [15]. The evidence to support this, however, is largely based on case reports. The high costs of some of these products may also be prohibitively expensive for regular usage. Thromboplastin, a natural blood-clotting agent obtained from bovine plasma, is available as a powder for topical application [16]. Systemic injection or absorption can lead to serious clotting. Absorbable gelatin is available as a sterile sponge-like dressing or sterile powder [17-19]. It can be applied dry or saturated with sterile sodium solution and is absorbed within 4-6 weeks. When applied, fibrin is deposited in the interstices of the foam, resulting in swelling of the sponge, thereby forming a large synthetic clot. When applied to nasal, rectal, or vaginal mucosa, it liquefies within 2-5 days. Other bioabsorbable topical hemostatic agents include fibrin sealants [20, 21] and Thromboplastin, a natural blood-clotting agent obtained from bovine plasma, is available as a powder for topical application [16]. Systemic injection or absorption can lead to serious clotting. Absorbable gelatin is available as a sterile sponge-like dressing or sterile powder [17-19]. It can be applied dry or saturated with sterile sodium solution and is absorbed within 4-6 weeks. When applied, fibrin is deposited in the interstices of the foam, resulting in swelling of the sponge, thereby forming a large synthetic clot. When applied to nasal, rectal, or vaginal mucosa, it liquefies within 2-5 days. Other bioabsorbable topical hemostatic agents include fibrin sealants [20, 21] and

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oxized cellulose [13]. Fibrin sealants are derived from human plasma and reproduce the final steps in the coagulation pathway to form a clot. They are used in a broad range of surgical procedures to assist hemostasis, including cardiovascular, hepatic, and splenic surgery. Some are impregnated with clotting factor XIII and a solution of thrombin and calcium chloride [9]. Collagen is another agent with inherent hemostatic activity. When applied as a bovine-derived mesh it comes into contact with blood, provokes the clotting cascade, and forms a clot [11, 12]. Alternatively, oxidized cellulose compounds and highly absorbent alginate dressings, derived from seaweed, are available for topical use [12, 14].

Vasoconstricting or cauterizing agents provide an alternative modality to managing localized, capillary-based bleeding. Epinephrine may be used, but its liberal use is discouraged [12]. Prostaglandins E2 and F2 have been used to control intractable hemorrhagic cystitis [22]. Bladder spasms, however, may limit their utility. Silver nitrate, an inorganic silver salt, induces a chemical cauterization and has been used to control bladder hemorrhages and epistaxis [12, 23]. Formalin, 2% or 4%, acts as a chemical cautery and has been used to control intractable rectal [24-26] and bladder [22] hemorrhaging. In one case series, topical formalin controlled bleeding in 49 of 55 patients (89%) with radiation-induced rectal bleeding. Aluminum astringents, such as 1% alum, can be delivered by continuous bladder irrigation [22]. Bladder spasms are controllable with antispasmodic medications. Sucralfate has shown some benefit in controlling cancer-related gastrointestinal bleeding and cutaneous ooze [15]. In the latter, a gel is prepared by dispersing one 1-g tablet of sucralfate in 5 ml of water soluble gel (e.g., K-Y Jelly; McNeil-PPC, Inc.; Skillman, NJ) and is applied once or twice daily [15].

Radiotherapy

External-beam radiotherapy has been shown to decrease hemoptysis caused by lung cancer, with control occurring in up to 80% of patients [27-30]. The optimal dose and fractionation remain controversial. Hypofractionation appears to be as effective as multiple fractions (often 10 or more daily fractions) [31-33]. A single fraction of 10 Gy has been shown to be as effective as multiple fractions in patients with hemoptysis due to lung cancer [29]. Total doses of either 20 Gy (via multiple fractions) or 8 Gy (via hypofractionation) are often suggested.

Radiotherapy should also be considered for bleeding from cancerous lesions of the vagina [29, 34], skin [35], rectum, and bladder [29, 36, 37]. External-beam radiotherapy may be successful in controlling bleeding in up to 85% of cases of rectal bleeding and 60% of cases of hematuria from bladder cancer [29, 36]. One study found that a hypofractionated regimen (17 Gy in two fractions over 3 days) for patients with symptoms from advanced bladder cancer was as well tolerated as and less distressing to patients than a regimen of 12 fractions given over 26 days (45 Gy) [36].

Upper gastrointestinal hemorrhaging from malignant processes is less amenable to radiotherapy. While radiotherapy can be useful in controlling bleeding from head and neck cancers, many of these patients have already received maximal doses of radiotherapy when they present with bleeding, thereby excluding further radiation [38]. Single or reduced fraction regimens appear to be as effective as multiple fractions in controlling bleeding [29].

Endoscopy

Endoscopy-based treatments have, for a long time, been used in managing bleeding from upper gastrointestinal varices, particularly after systemic therapies such as vasoconstricting or somatostatin analogues have failed. This treatment method has been reported to be superior to balloon tamponade [39]. It involves the injection of sclerosing agents into the varices or ligation of the vessels.

Endoscopic interventions have also been proven to be useful for managing cancer-related hemorrhaging of the upper gastrointestinal tract [40, 41], lungs [42-44], and bladder [45]. Ethanol [46, 47], hyperosmotic saline epinephrine [41], gelatin solutions [48], and sodium tetradecyl sulfate [41] are injected into the site of bleeding. Alternatively, the vessels may be cauterized by heat [47, 49], or by polar [47, 49] or laser coagulation [50, 51].

Akhtar and colleagues reported on a series of 48 consecutive patients with esophageal cancer who underwent endoscopic argon-beam plasma coagulation for symptom and disease control [40]. Bleeding was well controlled in three of the five patients treated for bleeding. Hemostasis was achieved in approximately 70%-90% [41, 49] of cases treated for upper gastrointestinal bleeds. Complications occurred in 5%-15% of cases and included worsening of the bleeding and perforation of the tract. Cystoscopic-assisted cautery by either heat or laser probes has been used in the treatment of hematuria in patients with bladder cancer [45]. Its role is mainly for patients in whom continuous bladder irrigation and lavage have failed. Under direct vision, the urologist can inspect the bladder, identify the source of bleeding, and fulgurate the bleeding vessel or tumor [22, 29, 45]. In the case of hemoptysis, bronchoscopy allows for ice-cold saline lavages [44] and/or the use of balloon tamponade [44, 52], laser phototherapy [44], or topical application of thrombin or fibrinogen at the site of bleeding [44]. Endoscopic procedures have been used to control bleeds from the lower gastrointestinal tract, although these may be more challenging [53, 54]. Colonoscopic techniques
vary and include bipolar electrocoagulation, heater probe, argon [55], and Nd:YAG lasers [54].

**Interventional Radiology**

Transcutaneous arterial embolization (TAE) may be useful in well-selected patients. The procedure is often performed via a femoral or axillary approach under local anesthetic and is generally well tolerated, requiring only mild sedation [56]. The blood vessel supplying the affected site is first identified by arteriography. This is followed by the insertion of a hemostatic agent, usually in the form of a coil. Limiting factors include the presence of a bleeding disorder and the availability of the appropriate expertise. Embolization is restricted to areas where the blood vessels are accessible by the catheter and where embolization of the blood vessel does not result in ischemia of key organs. Benefits have been reported in patients with cancers involving the head and neck [57-59], pelvis [60-64], lung [43, 44, 61, 65], liver [66], and gastrointestinal tract [67]. As with other treatment options in this setting, the majority of the evidence supporting this modality relies on case reports.

Nabi and team evaluated the efficacy of bilateral internal iliac artery embolization with permanent coils to control intractable hemorrhage from advanced pelvic urological malignancies [60]. Bleeding was controlled in all but one of six patients at the first attempt. The nonresponder was successfully treated at a second attempt. Complications were minor and included nausea, vomiting, and fever for a few days. At 22-month follow-ups, no patient had experienced bleeding recurrence.

TAE has been used to manage carotid artery rupture in cancer patients. Bates and Shamsham reported on a patient whose episodes of profuse (but self-limited) carotid hemorrhage were successfully controlled by an endovascular technique that combined placement of a flexible self-expanding stent-graft to protect the common and internal carotid artery with selective coil embolization of the affected external carotid artery branches [57]. Sakakibara and colleagues used an endoluminal balloon to control bleeding in three patients prior to undergoing surgical ligation of the arteries [58].

Transhepatic arteriobemobilization was used to control bleeding in five patients with inoperable hepatocellular cancer who presented with gastrointestinal bleeding from a variety of sources (esophageal varices or direct invasion of the duodenum, transverse colon, or stomach) [67]. Recordare and colleagues described four patients who underwent TAE to control spontaneous rupture of hepatocellular carcinoma [66]. Patients lived for 3-62 months following the procedure. A quality-of-life analysis was not reported. Wu and colleagues suggested that acute upper gastrointestinal bleeding is a potential complication following TAE in patients with hepatocellular cancer [68]. Thirty-one of 208 patients who underwent TAE in their service experienced upper gastrointestinal bleeding after the procedure. However, given that gastric or duodenal ulcers were found in 21 of these cases, Mallory-Weiss syndrome was found in three cases, and esophageal varices were found in two cases, the bleeding was likely the result of comorbidities and complications of the cancer rather than the treatment itself. Notwithstanding, the importance of meticulous case selection needs to be underscored.

**Surgery**

Surgery may be appropriate for a small group of well-selected patients who have failed conservative measures and who are deemed fit for surgery. Surgery usually consists of ligation of larger vessels [69] or the removal of bleeding tissue [70]. Two surgical approaches have been described for the management of carotid artery rupture: resection with reconstruction and ligation of the artery. Witz et al. reported on three patients with head and neck cancers who presented with acute or imminent carotid artery rupture [69]. Those patients successfully underwent ligation of the artery with no neurological sequelae. Vagappan and colleagues reported on prospectively collected data from 55 women who presented with bleeding from radiation proctitis [26]. Bleeding in six patients who did not respond to topical formalin application was controlled with surgery.

**Management: Systemic Interventions (Table 2)**

**Vitamin K (Phytonadione, Menadiol)**

Vitamin K is necessary for the hepatic production of a number of clotting factors, including factors II, VII, IX, and X. Liver disease, insufficient intake of leafy green vegetables (a source of vitamin K), small bowel disease or resection, as well as intrahepatic and extrahepatic biliary obstruction can

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lead to deficiencies in the clotting factors. Coagulation screening studies reveal a prolonged prothrombin time or international normalized ratio (INR) and partial thromboplastin time with normal thrombin time, fibrinogen, and serum fibrinogen degradation products.

Vitamin K treatment may be helpful if either a derangement of these factors or excessive warfarin therapy is implicated in bleeding in a patient with advanced cancer. Doses of 2.5-10 mg are recommended, depending on the severity of the situation. The jury is not out on which route of administration is best. Whitling et al. evaluated four different routes of vitamin K administration for reversing excessive anticoagulation: high-dose intravenous (1-10 mg), low-dose intravenous (≤0.5 mg), subcutaneous (1-10 mg), and oral (2.5-5 mg) [71]. Anticoagulation was achieved in all four groups. Although the high-dose intravenous method was the most effective at lowering INR levels to <5, overcorrection occurred more frequently with that method. Byrd and colleagues reported the effective and safe reversal of excessive warfarin anticoagulation using subcutaneous phytonadione at doses of 1 mg for INR levels >8 but <14 (group 1) and 2 mg for levels >14 (group 2) [72]. The mean INR reductions in group 1 and group 2 after 24 hours were 49% and 67%, respectively. By 48 hours, INR levels were below 4.5 in both groups. No hemorrhagic or thrombotic complications were reported. The subcutaneous administration of phytonadione did not correct the INR as rapidly or as effectively as intravenous administration in a randomized trial [73]. Higher doses of subcutaneous phytonadione were recommended for cases where full anticoagulation reversal is required. Nee et al. suggested that subcutaneous administration along with modification of the warfarin dosing is acceptable, since all patients in their study achieved safe levels of anticoagulation within 72 hours of subcutaneous administration [74]. A recent retrospective study of 105 patients reported that only two (1.9%) patients who received intravenous phytonadione experienced adverse reactions [75]. These anaphylactoid reactions manifest as dyspnea, chest tightness, facial flushing, nausea, and, in severe cases, cyanosis, loss of consciousness, hypotension, and possibly death. However, review of the literature reveals that these are rare occurrences [76].

A randomized, double-blind, placebo-controlled study comparing oral phytonadione (2.5 mg) plus the omission of further warfarin therapy with omission alone for reversing excessive warfarin anticoagulation in 30 asymptomatic patients (INR levels of 6-10) found that the addition of oral phytonadione reduced the time to achieve a normal INR by 1 day [77]. Adverse effects did not differ between the two groups. Fondevila et al., on the other hand, reported no advantage of adding oral phytonadione (1 mg) to a regimen of simply discontinuing the warfarin in patients with excessive oral anticoagulation [78]. Oral menadione (20 mg daily for 3 days) was found to be as effective as intravenous phytonadione (1 mg daily) in normalizing INR levels in 26 patients with cholestasis [79]. Therefore, when possible, vitamin K should be given by the subcutaneous or oral routes. When intravenous administration is considered unavoidable, the drug should be injected slowly, probably not exceeding 1 mg per minute. If, in 6-8 hours after parenteral administration, the INR is not satisfactorily lowered, the dose may be repeated. The role of prophylactic vitamin K administration for asymptomatic patients with elevated INR levels from liver involvement is unclear.

**Vasopressin/Desmopressin**

Vasopressin is a posterior pituitary hormone that causes splanchnic arteriolar constriction and reduction in portal pressure when injected intravenously or intra-arterially [80]. This method has been extensively used in managing variceal bleeding related to portal gastropathy [81, 82]. Its use has also been reported in oncology. In a controlled trial, vasopressin therapy stopped bleeding in about half the patients with active upper-malignancy-related gastrointestinal bleeding [83]. Doses range from 0.1-0.4 mg by continuous infusion. Vasoconstrictor effects on the myocardial, mesenteric, and cerebral circulation are the most notable potential side effects.

**Somatostatin Analogues**

Octreotide, an analogue of somatostatin, has been used to manage upper gastrointestinal bleeds [84]. Somatostatin reduces splanchnic flow and pressure via venous dilatation, thereby reducing portal pressure and portal venous flow. A starting dose of 50-100 µg twice daily is recommended [85]. The dose may be titrated, as needed, up to 600 µg per day. An alternative regime consists of a bolus of 50 µg given intravenously or subcutaneously, followed by a continuous subcutaneous or intravenous infusion of 50 µg/hour for 48 hours [86]. At low doses, very few side effects are reported, but at doses greater than 100 µg/hour, nausea, abdominal discomfort, and diarrhea may occur.

D’Amico et al., in a meta-analysis, concluded that emergency sclerotherapy should be used only after vasoactive drugs (octreotide, somatostatin, vasopressin, terlipressin), which are effective in approximately 83% of cases, have failed [82]. A more recent meta-analysis reported that ligation appears to be the most effective treatment for bleeding varices (effective in a mean of 91% of times, 95% confidence interval [CI] = 82%-96%): more effective than vasoconstrictive treatment (vasopressin/terlipressin, which were effective 69% of times, 95% CI = 62%-83%), vasoactive treatment (somatostatin/octreotide, 76%; 95% CI = 68%-83%), and...
sclerotherapy (81%; 95% CI = 72%-88%) [81]. The difference between ligation and sclerotherapy was not significant.

Except for preventing perioperative bleeding in pancreatic cancer resections [87], there are no reports related to the use of octreotide/somatostatin in controlling bleeding in cancer patients.

**Antifibrinolytic Agents**

Tranexamic acid (TA) and aminocaproic acid (EACA) are synthetic antifibrinolytic agents that block the binding sites of plasminogen, thereby inhibiting the conversion of plasminogen into plasmin by tissue plasminogen activator [88]. The end result is a decreased lysis of fibrin clots [89, 90]. Tranexamic acid is approximately 10 times more potent than EACA in vitro [91, 92]. Fibrinolytic inhibitors have been used successfully in a variety of nononcologic settings. These include the control of bleeding following dental extractions [93], subarachnoid hemorrhages [94], and gastrointestinal bleeds [95]. Several case reports and a few studies have been published that suggest a role for these agents in the oncology setting [88, 96-101].

TA and EACA have been administered orally and intravenously. The suggested intravenous dose of TA is 10 mg/kg three to four times a day, infused over about 1 hour. The suggested intravenous dose of EACA is 4-5 g in 250 ml over the first hour then 1 g/hour in 50 ml administered continuously for 8 hours, or until the bleeding is controlled [92]. The most common adverse effects are gastrointestinal in nature (nausea, vomiting, and diarrhea) and occur in 25% of cases [91]. Adverse effects appear to be dose dependent. Thromboembolism is uncommon [101, 102]. These antifibrinolytics can also be applied topically, rectally, or by intrapleural instillation [88, 97, 103].

A systematic review of randomized trials found that hemostatic medications (TA, EACA, desmopressin, and aprotonin) used for reducing surgery-related bleeding have limited or contradictory evidence of efficacy [104]. Large controlled studies of these drugs are lacking in the cancer setting.

**Blood Products**

The frequency and severity of hemorrhages increases as platelet count declines below 20,000/µl [105]. The risk of severe bleeding rises only when the count is below 5-10,000/µl. Patients with chronic autoimmune thrombocytopenia can tolerate platelet counts in the 5-10,000/µl range for long periods of time. Platelet transfusion in the setting of advanced cancer should be on a case-by-case basis with the aim of controlling symptoms [106]. A single unit of platelets should increase the platelet count in an average adult by approximately 6,000-10,000/µl, assuming normal splenic pooling. Four to six units are usually required to control bleeding. There is no scientific basis for the old 20,000/µl cutoff [107-110]. The short half-life of platelets, which decreases further as their counts drop, limits their usefulness in severely thrombocytopenic patients with end-stage disease. Lassauniere and colleagues have proposed criteria for platelet transfusions in patients with advanced hematologic malignancies [106]. These criteria include continuous bleeding of the mouth or gums, epistaxis, extensive and painful hematomas, severe headaches, or disturbed vision of recent onset, as well as continuous bleeding through the gastrointestinal, gynecological, or urinary systems.

The issue of whether or not to continue platelet transfusions in thrombocytopenic patients with end-stage disease poses an ethical dilemma. While ongoing transfusions may be futile, patients and families may perceive the cessation of transfusions as withdrawal of life-sustaining therapy. Sensitive and empathic discussions among patients, their families, and the attending physician and health team are essential to explore their expectations, fears, and concerns and to engage in advanced end-of-life planning while ensuring ongoing support and commitment to providing optimal comfort care.

Fresh frozen plasma is reserved for a very select group of patients with life expectancies greater than days to weeks. These include: A) patients with specific deficiencies in certain coagulation factors; B) patients in whom the effects of warfarin need to be reversed urgently; C) patients who require urgent invasive interventions such as thoracenteses or surgery; and D) when appropriate, the treatment of DIC. Similarly, packed red cell transfusions are indicated when anemia resulting from blood loss causes or aggravates symptoms such as fatigue and dyspnea. Guidelines for red blood transfusions in palliative patients have been published elsewhere [111, 112].

**End-of-Life Considerations**

The goals of care in a patient in the terminal phases of cancer should be comfort. Invasive treatments may present more burden than benefit in these patients, and comfort without invasive procedures takes precedence. In some cases, it is unclear as to whether or not a local or systemic measure will be of benefit. Time-limited or therapeutic trials (e.g., whether or not a platelet transfusion or an antifibrinolytic agent will provide benefit) may be warranted in select circumstances.

When a terminally ill patient is identified as being at risk for a major hemorrhage, family members and caregivers need to be sensitively informed and prepared, since these events can be extremely distressing. Using dark towels to absorb blood, applying pressure to the site of hemorrhaging, and placing patients in the lateral position (in the event of hematemesis or hemoptysis) are simple empowering...
measures. A rapid-acting sedative should be available for sedation. Midazolam, 2.5 mg or 5 mg intravenously or subcutaneously, serves this purpose well [1, 2]. If necessary, it can be repeated after 10-15 minutes. Orders for a sedative in case of such an emergency should be entered. Families/caregivers should be instructed on how to administer the medication subcutaneously. An indwelling subcutaneous butterfly facilitates administration. Families should be informed about whom to call in case of such an emergency. When patients have expressed a wish for comfort measures only, it would be inappropriate to call 911.

Anticoagulants should be reviewed, and the benefits versus burdens of continuing with these treatments should be considered. Maintaining therapeutic INR levels in terminally ill patients taking warfarin can be challenging and may require a switch to a low-molecular-weight heparin if the benefits of continuing anticoagulation outweigh the risks and burdens [113, 114]. The pharmacokinetics of these drugs are more predictable, their interactions with other drugs are less, they are not affected by liver dysfunction, and they require much less monitoring, negating the need for regular blood tests in these patients [113, 115].

**CONCLUSION**

Bleeding in patients with advanced cancer can be caused by a variety of underlying processes and presents clinically in many different ways, from chronic, low-volume bleeding to acute episodes of major hemorrhaging. Identifying the underlying cause(s) is an important first step in managing it. Whether the bleeding originates from capillaries or from larger vessels will affect the treatment plan. Several local modalities are available to manage localized bleeding. These include topical hemostatic agents and dressings, radiotherapy, endoscopic procedures, and TAE or balloon placement through interventional radiology. The use of interventional radiology is increasing. Systemic treatments are also available, particularly for more generalized bleeding or oozing. The majority of these treatments are supported only by case reports and series in the setting of advanced cancer. Comparative and controlled trials are lacking in this patient population. Patients at risk for major hemorrhages should be identified, and their families and caregivers should be prepared. End-of-life decision making should be based on comfort and the optimization of quality of life.

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