

# Putting Evidence Into Practice: Prevention and Management of Bleeding in Patients With Cancer

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The primary cause of bleeding in patients with cancer is thrombocytopenia and it commonly is attributed to myelosuppressive chemotherapy, radiation therapy, or bone marrow infiltration of the malignancy. Oncology nurses have a critical role to play in the prevention and management of bleeding in patients with cancer. As part of an Oncology Nursing Society Putting Evidence Into Practice (PEP) project team, the authors of this article reviewed the current literature to identify effective interventions in the prevention and management of bleeding in patients with cancer. The authors evaluated research studies conducted since 1991, current clinical practice guidelines, and systematic reviews. The literature was reviewed, synthesized, and developed into evidence tables that were ultimately published in a PEP card. All data were reviewed by experts in the field of thrombocytopenia. The Prevention of Bleeding PEP card was unveiled at the 8th Annual Institutes of Learning in November 2007.

**B**leeding in patients with cancer results from a complex interplay of disease and treatment-related factors. Bleeding may be the result of a reduction in the quantity or functional quality of platelets, an alteration in clotting factors, a paraneoplastic syndrome, or a combination of such factors. Thrombocytopenia is the primary cause of bleeding in patients with cancer and is commonly attributed to myelosuppressive chemotherapy, radiation therapy, or from bone marrow infiltration of the malignancy. Other causes of thrombocytopenia include splenic sequestration of platelets, immune-mediated thrombocytopenia, and platelet destruction from disseminated intravascular coagulation (DIC) (Avvisata, Tririndelli, & Kakanaporn, 2003).

Bleeding is manifested in several ways. Ecchymosis and petechiae can be presenting signs of thrombocytopenia and bleeding. More overt manifestations include epistaxis, hemoptysis, hematemesis, melena, hematuria, vaginal bleeding, and bleeding around wounds and vascular access lines. Although bleeding may occur slowly with continuous low-volume oozing, the potential for an acute cataclysmic event exists. Overall, the consequences of bleeding and subsequent hemorrhage may be profound with potential for hypovolemia, intracranial hemorrhage, and death (Pereira & Phan, 2004).

Nurses in the oncology outpatient and hospital setting often are the first to detect potential and actual bleeding issues and play a key role in the prevention of a catastrophic bleeding

event. To prevent and manage bleeding, nurses should use evidence-based interventions reflected in the published literature. Therefore, the purpose of this article is to provide nurses with current evidence about the prevention and management of bleeding in patients with cancer. The second purpose is to discuss the process and the development of the Prevention and Management of Bleeding Putting Evidence Into Practice (PEP) content from the Oncology Nursing Society (ONS).

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## At a Glance

- ◆ Bleeding in patients with cancer is caused by disease- and treatment-related factors that can range from mild to catastrophic (e.g., central nervous system hemorrhage).
- ◆ Oncology nurses play a key role in the prevention, early identification, and management of bleeding in patients with cancer.
- ◆ Nurses should be familiar with the evidence available on the prevention and management of bleeding and use it to help guide their decisions in clinical practice.

## Methods

The research team was comprised of two advanced practice nurses (one of whom was the project team leader), two researchers (one of whom was the lead researcher), two staff nurses, and an ONS staff member. The team's task was to critically examine and synthesize the literature on the prevention and management of bleeding in patients with cancer.

A systematic database search was conducted using CINAHL®, MEDLINE®, the Cochrane Collection, and UpToDate® to identify research studies, clinical guidelines, and articles related to the prevention and management of bleeding in patients with cancer. The search terms are listed in Figure 1. Database searches were performed by the project team leader, lead researcher, and the ONS information resources supervisor, a medical librarian. Multiple conference calls were conducted to establish the specific interventions to be included in the review of the literature and the subsequent recommendations for practice. Initially, citations from a six-year period (2000–2005) were searched and retrieved. However, because data were limited, the search was expanded to cover publications spanning the years 1991–2007. The team also manually searched reference lists in qualifying articles until saturation was reached. The abstract of each individual study was reviewed, and those meeting the inclusion criteria were selected for additional critique. Because a wide range of etiologies and consequences of bleeding can occur in the patient with cancer, the team chose to include evidence for interventions that prevent, ameliorate, or manage bleeding directly related to cancer or its treatment (e.g., surgery, chemotherapy, radiation, biotherapy). Selected inclusion criteria included the following.

- Sample included patients with cancer.
- Prevention and/or management of bleeding was the primary outcome in the clinical trial, guideline, or article.

Antifibrinolytics	Platelet transfusions
Bleeding	Prevention of bleeding
Hemorrhage	Thrombocytopenia
Hemorrhagic cystitis	Bleeding wounds
Management of bleeding	Nursing interventions and bleeding
Menorrhagia	
Platelet growth factors	

*Note.* All search terms were combined with *cancer*.

**Figure 1. Database Search Terms**

- Interventions included pharmacologic agents that were approved by the U.S. Food and Drug Administration. Excluded from the analysis were interventions that may not necessarily be related to the cancer or its treatment. Exclusion criteria included the following.
- Interventions used to prevent or treat the consequences of bleeding that may be related to noncancerous medical conditions, such as anemia, hypovolemia, or depletion of clotting factors.
- Interventions used to prevent or manage bleeding complications associated with comorbidities, such as gastrointestinal bleeding.
- Interventions to manage DIC, as this is most commonly observed as a result of sepsis or other noncancerous medical conditions.

## Critical Review of the Evidence

The members of the team divided the literature into three topical subgroups: antifibrinolytics and pharmacologic agents, blood products and nonpharmacologic agents, and procedures. Research studies were reviewed using a template developed by ONS including author(s), year of publication, characteristics of the intervention, sample characteristics, setting characteristics, study design, conceptual model, measures, results and conclusion, limitations including major and minor flaws, cautions and contraindications, special training needs, and costs. The lead nurse researcher guided the team through two reviews over a conference call to maintain consistency of the review procedures. Tables of evidence were organized by the following intervention categories or subcategories: platelet transfusions, prevention of hemorrhagic cystitis, prohemostatic agents, platelet growth factors, prevention of menstrual bleeding, procedures to prevent bleeding, and interventions to prevent and manage wound and orificial bleeding. After a thorough review of each article, the team collaboratively assigned two levels of evidence to each study or guideline: an eight-level rating by Hadorn, Baker, Hodges, and Hicks (1996), with one representing the highest level of evidence and eight representing the lowest level; and a three-level ONS rating, with one being the highest level of evidence and three being the lowest level (Ropka & Spencer-Cisek, 2001) (see Table 1).

## Highlights of the Reviewed Literature

About 150 research studies, guidelines, and articles were reviewed during the course of the project. Fifty-four met the inclusion criteria and were included in the review and compiled in the ONS Prevention of Bleeding PEP content according to one of six practice recommendation categories (see [www.ons.org/outcomes/tables/sleep/woe.shtml](http://www.ons.org/outcomes/tables/sleep/woe.shtml) for category descriptions). The studies, guidelines, and literature are synthesized in the following section and are nested in three categories: recommended for practice, likely to be effective, and expert opinion.

### Recommended for Practice

The recommended for practice category includes interventions for which effectiveness has been demonstrated by strong

**Table 1. Oncology Nursing Society (ONS) Levels of Evidence**

ONS LEVEL	LEVEL OF EVIDENCE	EVIDENCE SOURCE
I	1	Qualitative systematic review (also called integrative review) or quantitative systematic review (also called meta-analysis) of multiple, well-designed, randomized, controlled trials of adequate quality
I	2	At least one properly designed, randomized, controlled trial of appropriate size (record if multisite and over 100 subjects, but not required)
I	3	Well-designed trial without randomization (e.g., single group pre or post, cohort, time series, meta-analysis of cohort studies)
II	4	Well-conducted, qualitative, systematic review of nonexperimental design studies
II	5	Well-conducted case-control study
II	6	Poorly controlled study (e.g., randomized, controlled trial with major flaws) or uncontrolled studies (e.g., correlational descriptive study, case series)
II	7	Conflicting evidence with the weight of evidence supporting the recommendation or meta-analysis showing a trend that did not reach statistical significance National Institutes of Health Consensus Reports Published practice guidelines, for example, from professional organizations (e.g., Oncology Nursing Society, American Society of Clinical Oncology), healthcare organizations (e.g., American Cancer Society), or federal agencies (e.g., National Cancer Institute, Centers for Disease Control and Prevention)
III	8	Qualitative designs Case studies and opinions from expert authorities, agencies, or committees

*Note.* Levels of evidence range from the strongest evidence at the top to the weakest level of evidence at the bottom.

*Note.* From "PRISM: Priority Symptom Management Project Phase I: Assessment," by M.E. Ropka and P. Spencer-Cisek, 2001, *Oncology Nursing Forum*, 28(10), p. 1589. Copyright 2001 by the Oncology Nursing Society. Adapted with permission.

evidence from rigorously conducted studies, meta-analyses, or systematic reviews for which expectation of harm is small compared with the benefits.

**Platelet transfusions to prevent and manage bleeding:** The transfusion of platelets plays an active role in the prevention and management of bleeding. A review by Stanworth et al. (2004), clinical guidelines by the American Society of Clinical Oncology (ASCO) (Schiffer et al., 2001) and the Royal College of Physicians of Edinburgh (Norfolk et al., 1998; Schiffer et al.), a large systematic review by Heddle et al. (2006), and a smaller trial by Callow, Swindell, Randall, and Chopra (2002) comprised the evidence regarding the use of platelet transfusions in patients with cancer.

Stanworth et al. (2004) included eight related studies (N = 752) with 390 patients in platelet transfusion intervention groups and 362 patients in control groups. The authors acknowledged a lack of randomized, clinical trials in this body of literature; however, the overall conclusion from the analysis was to maintain a prophylactic platelet threshold of 10 x 10<sup>9</sup>/L in patients with cancer.

Norfolk et al. (1998) and Schiffer et al. (2001) provided additional supporting evidence for the threshold level. The ASCO panel of experts conducted a Medline search and then met, reviewed, and discussed platelet transfusion literature from the past 20 years reviewing the benefits versus harms of this approach. Outcome measures included prevention of morbidity and mortality from hemorrhage, overall survival, quality of life, toxicity reduction, and cost effectiveness. The panel used a level of evidence table to develop, rate, and grade recommendations for practice. The risk of bleeding was found to greatly increase

in patients with cancer when the platelet count was less than 10 x 10<sup>9</sup>/L. In addition, transfusions were found to reduce morbidity and death resulting from thrombocytopenia. The authors concluded that the risk of bleeding was still strong in patients with platelet counts less than 10 x 10<sup>9</sup>/L with or without platelet transfusions. The Royal College of Physicians of Edinburgh (Norfolk et al.; Schiffer et al.) developed a consensus statement with similar platelet threshold levels already noted.

Only two studies (Callow et al., 2002; Heddle et al., 2006) were found in the literature after the publication of the ASCO guidelines. The findings of the newer studies provided additional evidence for the ASCO-established platelet threshold levels. Callow et al. concluded that a platelet transfusion threshold of less than 10 x 10<sup>9</sup>/L in the absence of fresh bleeding and sepsis is safe. Heddle et al. conducted a secondary analysis and looked at bleeding risk in thrombocytopenia. An eight-fold increase in bleeding resulted when the platelet count was between 5-14 x 10<sup>9</sup>/L compared to 20-29 x 10<sup>9</sup>/L.

Overall, agreement exists that prophylactic platelet transfusions are likely to prevent and manage bleeding in patients with cancer who have thrombocytopenia or who are actively bleeding. Transfusion practices should reflect guidelines provided by ASCO (see Figure 2). Although the guidelines direct current practice, limitations are noted. The trials lacked scientific rigor and primarily were reviews in practice patterns using specific platelet threshold levels. The data also lacked inclusion of other important clinical variables that may have contributed to a patient's transfusion response and risk of bleeding. The largest samples included patients with acute leukemia or those undergoing hematopoietic stem cell transplantation (Callow et al.,

- Treat patients with platelets when significant hemorrhage and severe thrombocytopenia are present.
- The threshold for prophylactic platelet transfusion for adult patients receiving therapy for leukemia and for those undergoing stem cell transplantation is  $10 \times 10^9/L$ .
- The risk of bleeding in patients who have solid tumors and chemotherapy-induced thrombocytopenia is related to the depth of their nadir. Expert clinical opinion suggests a threshold of  $10 \times 10^9/L$  for prophylactic platelet transfusions in patients with solid tumors.
- The threshold for prophylactic platelet transfusion for patients undergoing minor procedures (e.g., bone marrow aspiration) and patients with bladder tumors, necrotic tumors, and those likely to bleed is recommended at  $20 \times 10^9/L$ .
- According to expert opinion, thrombocytopenic patients who require an invasive diagnostic or therapeutic procedure such as placement of a central venous catheter, endoscope with biopsy, bone marrow biopsies, or surgery may have them performed safely when the platelet count is in the range of  $40\text{--}50 \times 10^9/L$ .

## Figure 2. American Society of Clinical Oncology Platelet Transfusion Guidelines

Note. Based on information from Schiffer et al., 2001.

2002; Heddle et al., 2006). Studies including patients with solid tumors are lacking.

These studies have direct implications to nursing practice. Platelet transfusion threshold guidelines are recommended. Although the platelet count is the best available indicator of the potential risk of bleeding in a patient with cancer, other key clinical factors should be considered. In addition to level of thrombocytopenia, the nurse should assess all patients for frank or occult bleeding and recognize that the platelet threshold for transfusion support may need to be adjusted in patients at risk for hemorrhage, with rapidly declining platelet counts and/or coagulation abnormalities, as well as other clinical correlates that may impact platelet functions, such as uremia. Two common scales used to quantify bleeding are the World Health Organization (WHO) bleeding scale (see Figure 3) and the Common Terminology Criteria for Adverse Events (v.3.0) (CTCAE) from the National Cancer Institute (see [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/ctcae3.pdf](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf)). The CTCAE is descriptive terminology that can be used for a variety of adverse event reporting. The quantification of bleeding is an important clinical variable to consider when determining the need for prophylactic or therapeutic platelet transfusion support.

**Prevention of hemorrhagic cystitis:** Hemorrhagic cystitis (HC) is an adverse effect of ifosfamide and cyclophosphamide chemotherapy. The exact incidence of HC is unknown and depends on whether the HC is chemotherapy or radiation therapy induced. One professional guideline and two clinical trials provide recommendations for practice for the prevention of HC. The professional guidelines by ASCO were developed by a multidisciplinary expert panel that reviewed literature spanning June 1997 through December 1998 (Hensley et al., 1999). The guidelines underwent a revision and included literature through 2001 (Schuchter, Hensley, Meropol, & Winer, 2002). The experts rated data according to the level of evidence and each practice

was given a grade for recommendation, ranging from A to D, with A indicating the highest level of evidence and D indicating the lowest level. Figure 4 includes a summary of the current ASCO guidelines. Please note that the ASCO guidelines were published in 2001 and, although the panel indicated it would reconvene every three years, no follow-up guidelines have been published to date.

Additional clinical trials have been published since the 2001 ASCO guidelines. Tsuboi et al. (2003) conducted a large clinical trial to evaluate the most appropriate therapy for HC following stem cell transplantation in patients treated with high-dose cyclophosphamide. The authors concluded that mercapto ethane sulfonate sodium (MESNA) may actually be toxic to the bladder and may be associated with the onset of HC. The data are in conflict with other studies that show a bladder protective effect with MESNA.

Khojasteh, Zakerinia, Ramzi, and Haghshenas (2000) conducted a prospective, experimental, nonrandomized trial, examining whether more frequent MESNA administration (at baseline, 1, 3, 5, 8, 11, 14, 17, and 20 hours) prevented HC in patients ( $N = 11$ ) undergoing allogeneic bone marrow transplantation. Four of the 11 patients developed HC despite frequent MESNA administration. However, the study was limited by a small sample size.

In summary, MESNA is recommended for the prevention of ifosfamide-induced HC. MESNA plus saline diuresis or forced saline diuresis is recommended for cyclophosphamide administration in the stem cell transplantation setting. Recommendations for practice remain consistent with ASCO guidelines.

## Effectiveness Not Established

The effectiveness not established category of evidence includes interventions for which insufficient or conflicting data or data of inadequate quality exist, with no clear indication of harm.

**Prevention of hemorrhagic cystitis with agents other than MESNA:** Limited evidence exists that agents other than MESNA can prevent HC. Several studies (Srisupundit et al., 1999; Veerasarn, Boonnuch, & Kakanaporn, 2006; Veerasarn et al., 2004) examined the use of chlorite-matrix, also known as WF 10, for HC. The three trials included women patients

### Grade 0

No bleeding

### Grade 1

Petechiae, ecchymosis, occult blood in body secretions (e.g., guaic plus stool), and mild vaginal bleeding

### Grade 2

Evident blood loss such as epistaxis, hematuria, and hematemesis not requiring additional transfusion support

### Grade 3

Gross blood loss or hemorrhage requiring transfusion support

### Grade 4

Life-threatening hemorrhage (massive bleeding with hemodynamic compromise, and/or bleeding into a vital organ, such as intracranial)

## Figure 3. World Health Organization Bleeding Scale

Note. Based on information from Slichter, 2004.



- MESNA should be used to decrease urothelial toxicity associated with ifosfamide infusion.
- If ifosfamide is dosed at less than 2.5 g/m<sup>2</sup> per day, the dose of MESNA is recommended at 60% of the ifosfamide dose and should be given 15 minutes before chemotherapy and then at four and eight hours following each dose of ifosfamide.
- If ifosfamide is given via continuous infusion, then MESNA should be given prior to chemotherapy as a bolus dose at 20% of the ifosfamide dose followed by a continuous infusion of MESNA at 40% of the ifosfamide dose and continuing 12–24 hours after the completion of the ifosfamide infusion.
- Insufficient evidence exists to recommend a specific dosing regimen for the use of MESNA with high-dose ifosfamide in excess of 2.5 g/m<sup>2</sup> per day. More frequent and/or prolonged MESNA dosing regimens may be necessary to achieve urothelial protection, given the longer half-life of ifosfamide at higher doses.
- Oral MESNA may be used for the second and third doses when the ifosfamide dose is less than 2 g/m<sup>2</sup> per day. When using oral MESNA, the first dose should be given IV at 20% of the ifosfamide dose followed by oral doses of MESNA at 40% of the second and sixth ifosfamide dose. The total daily dose of MESNA is 100% of the ifosfamide dose. Patients who vomit within two hours of taking oral MESNA should have the oral dose repeated or should receive IV MESNA. This dosing schedule is repeated on each day that ifosfamide is given.
- MESNA plus saline diuresis or forced saline diuresis is recommended for cyclophosphamide administration in the stem cell transplantation setting.

#### Figure 4. American Society of Clinical Oncology Guidelines for Mercapto Ethane Sulfonate Sodium (MESNA) Use With Ifosfamide Infusion

Note. Based on information from Hensley et al., 1999.

undergoing radiation therapy for a gynecologic malignancy. The complete response (CR) rate ranged from 30%–76%, whereas the partial treatment response (PR) ranged from 50%–88%.

Srisupundit et al. (1999) included an intervention of WF 10 0.5 ml/kg given IV to 20 patients with grade 3 radiation cystitis who did not respond to standard treatment. Patients who had a PR or no response (NR) to the initial treatment were given a second cycle after a 7- to 14-day rest period. Six patients (30%) had a CR within 5–10 days, 10 (50%) had a PR, and four (20%) had NR. Seven PRs and two non-responders received a second cycle of WF 10; three patients went on to a CR and four patients had a PR. Only two patients had NR after two cycles. Eighteen patients from the CR and PR groups were evaluated at nine months; 13 had no signs of recurrent bleeding and five patients were lost to follow-up. The small sample size limited the level of evidence of this study.

Veerasarn et al. (2004, 2006) conducted two separate trials using WF 10 therapy (0.5 ml/kg) administered over two hours on five consecutive days every three weeks for two cycles from radiation. The 2004 trial was a randomized, placebo controlled, multicenter study comparing WF 10 to placebo in patients (n = 100) with grade 2–3 late HC from radiation (Veerasarn et al., 2004). Results indicated that 74% in the WF 10 group and 64% in the control group had an objective CR. Subjective hema-

turia decreased from grade 2 or higher to grade 0–1 in 77% of the WF 10 group versus 65% in the control group. Recurrent hematuria also occurred faster in the control group. Cystoscopy at one year showed improvement in both groups (the difference was not significant).

The 2006 trial was an open-label study of women treated with the WF 10 therapy for cystitis (n = 16) or proctitis (n = 14) from radiation. Eighty-eight percent of patients with cystitis showed improvement from a higher grade (2–4) to grade 0–1, and 77% of patients with proctitis also showed improvement. All patients responded within three months. Whether time or the intervention assisted in the healing process is uncertain. Additional investigation is needed to measure and understand the effectiveness of this intervention.

**Treatment of hemorrhagic cystitis:** A case study by Dorticus et al. (2003) described an intervention to treat HC. Epidermal growth factor hormone (rhEGF) was used as a cytoprotective bladder agent in a 15-year-old boy who was post-allogeneic bone marrow transplantation and who had developed hematuria with clots. After numerous other attempts to stop the bleeding, rhEGF was administered on day 51 after transplantation at a dose of 2 mg per day via continuous bladder irrigation and increased to 5 mg per day by day 55. After four days of rhEGF therapy, gross and microscopic bleeding stopped and the rhEGF was tapered on day 67. A five-month follow up showed no recurrence of HC. Although results of this case study are positive, additional studies are warranted.

Several nursing implications are evident for the prevention and risk reduction of HC. Appropriate intervention depends on the risk of HC associated with the causative agent and dose. Optimal hydration with careful monitoring of fluid intake and output is critical. In addition, ifosfamide should be administered with MESNA to prevent HC. Saline diuresis and/or MESNA should be used when administering cyclophosphamide in the stem cell transplantation setting. Also, ongoing monitoring is essential to detect early HC issues to prevent additional complications (Schuchter et al., 2002).

**Prohemostatic agents:** A number of single-arm trials and small case series report the use of prohemostatic agents to prevent and manage bleeding in patients with cancer. Hemostatic agents are substances that can be used to stop bleeding by shortening the clotting time and promoting clot formation.

**Desmopressin:** Castaman et al. (1997) conducted a small, single-arm pilot study to investigate the use of desmopressin in the prevention or treatment of bleeding in patients with hematologic malignancies (n = 15). In all cases, epistaxis or gum bleeding was stopped with 0.3 mcg/kg of desmopressin given IV over 30 minutes. Although successful for this small sample, no additional studies were found in the literature to support the agent's use.

**Tranexamic acid:** The use of tranexamic acid (TA) was investigated in a randomized, placebo-controlled trial in 38 patients with acute myeloid leukemia receiving induction with cytarabine and daunorubicin or consolidation with cytarabine (Shpilberg et al., 1995). The TA was administered every six hours to 16 patients in the TA group. Severity of bleeding was measured on a scale of 0–3, with 0 indicating no bleeding and 3 indicating major bleeding. No difference was noted during induction between the experimental and control groups regarding the period of thrombocytopenia (less than 20), number of

bleeding episodes, number of platelet or red blood cell transfusions, or score of bleeding events. However, during consolidation, the experimental and control groups saw no difference regarding period of thrombocytopenia. Bleeding events scored higher, were more severe, and led to a greater number of platelet transfusions in the control group (9.3 +/- 3.3) versus the treatment group (3.7 +/- 4.1) ( $p < 0.05$ ). No significant difference was noted in the number of red blood cell transfusions, and no thromboembolic or fatal bleeds occurred in either group.

Dean and Tuffin (1997) conducted a pilot study that examined the use of TA ( $n = 10$ ) or another prohemostatic agent, epsilon aminocaproic acid (EACA) ( $n = 6$ ), in patients with tumor-associated hemorrhage. The agent was chosen according to availability at each hospital. Bleeding ceased in 14 of the 16 patients. Several study limitations were noted, including a small sample size, inconsistent dose and duration of EACA and TA, and lack of a consistent definition of bleeding.

**Epsilon aminocaproic acid:** Three additional studies using EACA were investigated in the prevention of bleeding in patients with cancer. A study by Amar et al. (2003) aimed to reduce perioperative and intraoperative blood loss in patients with cancer undergoing orthopedic surgery. Sixty-nine patients were enrolled in the randomized, double-blind, placebo-controlled trial that compared EACA, IV aprotinin, and placebo. The EACA and aprotinin treatment groups had significantly lower D-dimer levels ( $p < 0.01$ ) 48 hours after surgery, which confirms the antifibrinolytic effects of these two agents when compared to placebo.

A retrospective analysis by Kalmadi, Tiu, Lowe, Jin, and Kallaycio (2006) explored the effect of EACA in reducing platelet transfusions in patients with cancer with thrombocytopenic hemorrhage. Seventy-seven patients in the database received 4–6 g EACA per day for a median of eight days. Sixty-six percent of patients had a CR, 17% had a PR, and 17% had NR. Dose was not correlated with response, and patients with alloimmunization to platelet transfusions had a lower probability of response. A decrease in the number of platelet transfusions given compared to those in the database who did not receive EACA was noted. Adverse effects included worsening of liver function tests, genitourinary clots, atrial fibrillation, nausea, and orthostatic hypotension.

In a study by Wanko, Broadwater, Folz, and Chao (2006), EACA was administered to allogeneic transplantation recipients with diffuse alveolar hemorrhage not responding to solumedrol. Although 14 patients enrolled in the study, eight did not respond to the solumedrol and were given EACA 1,000 mg IV every six hours. The 100-day mortality rate of diffuse alveolar hemorrhage improved significantly, from 83%–44%, in patients treated with EACA (Wanko et al.).

**Recombinant activated factor VIIa:** Recombinant activated factor VIIa (rFVIIa) is another prohemostatic agent that has been investigated to prevent and manage bleeding in patients with cancer. An analysis by Brenner et al. (2005) examined patients registered in an international database who had thrombocytopenia and were given 18–1,040 mcg/kg rFVIIa to manage hemorrhage ( $n = 24$ ). Individual clinicians classified the bleeding as mild, moderate, or severe. Bleeding stopped in 46% of the patients, markedly decreased in 33%, and decreased in 17%. One patient had an ischemic stroke possibly related to rFVIIa, and three deaths were felt to be related to bleeding. This Web-based study was limited by

incomplete patient histories, dose variations, comorbidities, and minimal follow up (Brenner et al.).

A case study by Hicks, Peng, and Gajewski (2002) was reported in the literature using rFVIIa at 90 mcg/kg every three hours for four doses along with high-dose corticosteroids in a patient with acute myelogenous leukemia and diffuse alveolar hemorrhage following bone marrow transplantation. The case study patient had previously been unresponsive to treatment with EACA and fresh frozen plasma. Bleeding stopped after the third dose of rFVIIa and radiographic and clinical status improved.

In another study using rFVIIa (Lodge et al., 2005), 204 patients undergoing non-cirrhotic partial hepatectomy for cancer and/or benign tumors were randomized to receive rFVIIa in doses of 20 mcg/kg, 80 mcg/kg, or placebo. Results indicated a decrease in blood loss during surgery ( $p = 0.07$ ) and a decrease in perioperative red blood cell transfusion requirements approached significance ( $p = 0.09$ ).

Although the evidence for prohemostatic agents is building, insufficient evidence exists from the lack of well-conducted randomized, controlled trials with adequate sample sizes (i.e., more than 100). The evidence is not established, but nurses should recognize this as a potential intervention that may assist in the prevention and management of bleeding.

**Recombinant human interleukin-11:** Recombinant human interleukin-11 (rhIL-11) is a growth factor that increases platelet production by stimulating megakaryocyte proliferation and maturation. rhIL-11 is approved by the FDA for the prevention of severe thrombocytopenia and reduction of the need for platelet transfusions in patients receiving myelosuppressive chemotherapy, therefore keeping chemotherapy doses on time (Tsimberidou et al., 2005). A multicenter, randomized, placebo-controlled trial was conducted in 93 patients with solid tumors or lymphoma previously transfused for severe thrombocytopenia (Tepler et al., 1996). Patients were randomized to receive 25 or 50 mcg/kg of rhIL-11 or placebo subcutaneous daily. Thirty percent of patients on the 50 mcg/kg dose did not require platelet transfusion compared to 18% with the 25 mcg/kg dose and 4% on placebo ( $p < 0.05$ ). Common side effects were fatigue and cardiovascular symptoms, including atrial fibrillation and syncope.

A randomized, blinded study by Isaacs et al. (1997) examined the safety and efficacy of 50 mcg/kg per day subcutaneous rhIL-11 versus placebo in 77 women with breast cancer undergoing chemotherapy. rhIL-11 administration began on day 2 of the chemotherapy cycle and continued for a minimum of 10 days. Sixty-eight percent of patients in the rhIL-11 group did not require platelet transfusions compared to 41% in the placebo group ( $p = 0.04$ ). Common side effects included mild peripheral edema, mild dyspnea, pleural effusion (patients with stage 4 disease), and conjunctival injection.

In a pediatric study of patients with solid tumors or lymphoma (Cairo et al., 2005), rhIL-11 was administered in doses of 25–125 mcg/kg per day on days 6–33 following two- to five-day cycles of chemotherapy. The maximum tolerated dose was determined to be 50 mcg/kg per day. Doses of 75 mcg/kg per day or higher resulted in tachycardia, conjunctival injection, edema, pain, rhinitis, diarrhea, cardiomegaly, papilloedema, and periosteal bone changes. Limits of this non-randomized study are the wide range of doses given and the patient inclusion range of up to 24 years of age.

## Updates to the Prevention of Bleeding Putting Evidence Into Practice Card

The Oncology Nursing Society's (ONS's) Prevention of Bleeding Putting Evidence Into Practice (PEP) card, along with ONS's other PEP cards, has been updated with new evidence that has been released since the card was developed. The full revision is now available in Eaton and Tipton (2009). All of the articles initially reviewed were re-rated with the PEP weight-of-evidence classification schema, an update from the ONS rating system. After reviewing the literature between January 2007 and November 2008, a total of seven additional articles were found that related to the prevention and management of bleeding in the patient with cancer. However, none of the articles met the weight-of-evidence classification schema criteria.

Eaton, L.H., & Tipton, J.M. (Eds.). (2009). *Putting Evidence Into Practice: Improving oncology patient outcomes*. Pittsburgh, PA: Oncology Nursing Society.

In two smaller, non-randomized studies (Kurzrock et al., 2001; Tsimberidou et al., 2005), patients with myelodysplastic syndrome, aplastic anemia, graft failure, post-chemotherapy aplastic anemia, refractory anemia, and bone marrow failure after transplantation were given lower doses of rhIL-11 (10 mcg/kg) subcutaneously daily for two weeks. Results indicated an increase in platelet levels with the lower doses and tolerable side effects including mild peripheral edema, conjunctival injection, fatigue, myalgia, arrhythmia, and transient ischemic attack (Kurzrock et al.; Tsimberidou et al.).

Although platelet growth factors may maintain platelet counts during chemotherapy, effectiveness in the prevention of bleeding has not been established. When encountered in the clinical arena, nurses should monitor fluid retention side effects along with bleeding.

**Interventions to prevent or attenuate menstrual bleeding:** Hormonal methods are effective in preventing menstruation; however, few studies specify patients with cancer. It may be common practice to induce amenorrhea and prevent menorrhagia in patients with anticipated grade 4 thrombocytopenia, but the effectiveness of such interventions are not established in the research literature. One retrospective clinical study (Meirow et al., 2006) explored the use of hormonal methods in 101 women who developed severe thrombocytopenia. Patients were grouped into those who received depo-medroxyprogesterone acetate, luteinizing hormone-releasing hormone agonist (GnRH-a), or no treatment for suppression of menstruation. The treatment groups were found to be superior to no treatment for the prevention of severe menorrhagia, but the difference between the two treatment groups was not statistically significant.

Another retrospective study (Amsterdam et al., 2004) reviewed the management of menorrhagia in women patients undergoing bone marrow transplantation who were referred to the gynecology service. Patients were treated with a variety of oral contraceptives, and 97% of patients achieved resolution of menorrhagia. Although the results supported the use of oral contraceptives to prevent menorrhagia in patients undergoing bone marrow transplantation, specific recommendations regarding doses of oral contraceptives were not made.

A small study by Chiusolo et al. (1998) supported using a lower dose of leuprolide to prevent menstruation in patients undergo-

ing stem cell or bone marrow transplantation. A dose of 3.75 mg at least one month before transplantation and repeated 28 days later was found to be effective. Although this study indicated some effectiveness, the data were limited by the small population (Chiusolo et al.).

The studies mentioned here support the continued practice of inducing therapeutic amenorrhea in patients with anticipated grade 4 thrombocytopenia, and nurses should anticipate this in clinical practice. A list of commonly used agents include oral contraceptives, progesterone, a progestin intrauterine device, GnRH-a, and danazol. However, randomized, placebo-controlled trials with large sample sizes are lacking and, therefore, effectiveness of these interventions is not established in the literature.

## Procedures to Attenuate Bleeding

**Therapeutic endoscopic procedures:** Endoscopic procedures that are pertinent to the prevention and management of bleeding in patients with cancer include the use of self-expandable metallic stents (SEMS) and endoscopic band ligation.

Several studies described the use of SEMS for patients with esophageal cancer (Iraha et al., 2006; Johnsson, Lundell, & Liedman, 2005; Siersema, 2005; Wenger et al., 2005). Small samples and the descriptive designs of these studies limit their level of evidence. Few addressed the use of SEMS in the prevention or management of bleeding directly. Iraha et al. used SEMS to alleviate dysphasia. Johnsson et al. used SEMS to treat esophageal perforations, thereby preventing hemorrhage. Siersema (2006) reviewed studies published in 2005 that addressed endoscopic therapeutic esophageal interventions, concluding that endoscopic band ligation was the most optimal technique for the treatment of varices.

**Endovascular embolization procedures:** Radiological endovascular embolization is a viable alternative to arterial ligation in the challenging group of patients with head and neck cancer who present with severe hemorrhage. Kakizawa, Toyota, Naito, and Ito (2005) examined embolization procedures using gelatin sponge particles, steel and/or platinum coils, or a combination of these embolic materials in 10 patients with head and neck tumors who were experiencing oral hemorrhage. Because open surgical exploration with ligation of the hemorrhaging vessels is difficult and dangerous, in this small study, superselective embolization of the affected arteries with the use of a microcatheter system was shown to be an effective, safe, and repeatable treatment for the control of oral hemorrhage caused by malignant head and neck tumors.

A retrospective review by Desuter et al. (2005) of two cases of patients with head and neck cancer presenting with a carotid blowout showed that management of a carotid blowout with endovascular stent placement can be successful. Bleeding was effectively stopped by the procedure in both cases, although the patients developed a post-procedure thromboembolism, which was immediately treated by anticoagulation therapy. A covered stent, combined with preliminary coiling, was used in these patients.

Microcoils and microparticles were used as embolization agents in a seven patient chart review reported by Sesterhenn, Iwinska-Zelder, Dalchow, Bien, and Werner (2006). All patients were successfully treated with this type of endovascular embolization (Sesterhenn et al.).



**Ultrasound-activated surgical instruments:** Lumachi et al. (2004) performed axillary dissection on patients with breast cancer by using ultrasound scissors. This prospective, randomized trial was conducted on 92 women with the surgeons either using ultrasound scissors (n = 45) or not using ultrasound scissors (n = 47). The use of ultrasound cutting devices were shown to reduce the risk of seroma formation (20% versus standard 40% seroma rate).

## Expert Opinion

Interventions in the category of expert opinion include low-risk interventions that are consistent with sound clinical practice, suggested by an expert in a peer-reviewed publication (journal or book chapter), and those for which limited evidence exists. An expert is an individual who has published articles in a peer-reviewed journal in the domain of interest.

**Nonpharmacologic interventions:** The literature on non-pharmacologic interventions to prevent or control bleeding in patients with cancer is limited and what is published addresses the prevention or control of bleeding in wounds. Numerous recommendations exist to control bleeding in malignant wounds (Gabay, 2006; Pereira & Phan, 2004; Seaman, 2006). Unfortunately, no trials exist that evaluate the effectiveness of these interventions. A summary of the recommendations for wound and orificial bleeding is included in Figure 5. Seaman recommended ice packs, elevating the affected area, applying direct pressure to the bleed (e.g., sandbag or IV bag to an oozing central venous catheter site), and topical hemostatic agents when bleeding continues. Hemostatic agents, in general, refer to any agent that promotes hemostasis, or the cessation of bleeding. These agents work in various ways in the intrinsic and extrinsic clotting pathways by interacting with platelets, coagulation factors, and the vessel wall (Gabay). Hemostatic agents can take many forms and have numerous applications and a full discussion of these varied agents is beyond the scope of this article. For the practicing oncology nurse, one of the more likely hemostatic agents to be used in the management of mild bleeding is topical thrombin. This product is indicated to manage minor bleeding, usually associated with capillary blood loss, such as mild epistaxis, and may be used in conjunction with an absorbable gelatin sponge product such as Gelfoam® (Pfizer, Inc.), which itself has hemostatic properties. In addition to topical thrombin, gauze also can be saturated with vasoconstrictors, such as epinephrine or sucralfate, for control of minor bleeding (e.g., nasal packing for uncontrolled epistaxis), and silver nitrate sticks can be used for smaller bleeding areas (Seaman). None of these interventions have been systematically evaluated for practice but may be indicated for patient comfort and to control minor bleeding.

Pereira and Phan (2004) recommended minimizing the frequency of dressing changes to prevent trauma in fragile tissue prone to bleeding, using saline when changing dressings to prevent adherent tissue from bleeding, and using moist wound products if the wound does not have a lot of exudates. If bleeding in wounds does occur and is not amenable to interventions, hemostatic and/or vasoconstrictive agents may be employed. These pharmacologic agents are applied to control local bleeding, either topically or via packing (e.g., nasal packing with saturated gauze) (Pereira & Phan). Case reports reveal that

### Wound Care Interventions

- Gentle dressing removal using saline if the dressing adheres to the wound
- Nonadherent or amorphous dressings or moist wound products
- Multiple layer dressings to prevent wound trauma
- Direct pressure for 10–15 minutes when bleeding occurs
- Packing with or without pressure (in nose, vagina, or rectum)
- Minimization of the frequency of dressing changes to prevent trauma

### Hemostasis Interventions

- Gauze saturated with topical vasoconstrictors (epinephrine to control profuse bleeding) or sucralfate paste
- Packing swabs containing hemostatic agents (acetone in vagina or cocaine in nose)
- Topical dressings, including the use of thromboplastin, absorbable gelatin (in nose, rectum, or vagina), fibrin sealants, collagen, or alginate
- Vasoconstricting or cauterizing agents (epinephrine, silver nitrate, formalin, or alum)

## Figure 5. Recommendations to Prevent Wound and Orificial Bleeding

*Note.* Based on information from Gabay, 2006; Pereira & Phan, 2004; Seaman, 2006.

absorbable hemostatic agents also may be useful when surgical bleeding cannot be controlled by conventional methods such as pressure (Gabay, 2006).

**American Red Cross guidelines:** The 2006 American Red Cross first aid guidelines (American Heart Association & American National Red Cross, 2005) recommended direct pressure over the bleeding area, but elevation and the use of pressure points are no longer recommended. Please note that the recommendations are first aid guidelines and are not cancer specific.

## Summary

Bleeding is a common complication in patients with cancer. Although bleeding may be minor in some cases, it has the potential to become a catastrophic oncologic emergency. Bleeding in patients with cancer is multifactorial and can occur because of the primary cancer and also secondary to treatment. A key intervention in the prevention and management of bleeding in patients with cancer is the judicious use of prophylactic and therapeutic platelet transfusions because of the well-established association between bleeding and thrombocytopenia. A strong evidence base exists to guide the use of platelet transfusions, and oncology nurses should be knowledgeable of the recommended guidelines for platelet transfusions, including threshold platelet levels.

Certain cancer treatments (ifosfamide and cyclophosphamide) carry a well-defined risk of urothelial toxicity that can result in HC. Nurses caring for patients receiving these therapies should be knowledgeable of the recommendations for the use of the cytoprotective agent MESNA to prevent ifosfamide-associated HC. HC also is an untoward complication in patients receiving pelvic irradiation; however, insufficient evidence exists to recommend any standard intervention to



## The American Red Cross First Aid and CPR Recommendations

The American Red Cross has worked to implement newly released first aid and CPR guidelines into its training and educational programs. One of the most significant changes was the way in which individuals are instructed to control bleeding. Control of bleeding is one of the few actions that a person can critically influence the outcome in a first aid situation. The old recommendation, according to the *First Aid and CPR Guidelines 2005*, for control of bleeding was using a combination of direct pressure, elevation, and pressure points to stop the bleeding. The guidelines now recommend that applying direct pressure firmly over the bleeding area until the bleeding stops or emergency rescuers arrive is the more effective way to control bleeding. The methods of pressure include the following.

- Use manual pressure on gauze or other cloth placed over the source of bleeding; add more gauze or cloth and pressure if the bleeding persists.
- Use an elastic bandage firmly wrapped over gauze to hold it in place with pressure.

*Note.* Based on information from American Heart Association & American National Red Cross, 2005.

prevent radiation-induced HC. The evidence to support effective treatment of HC (regardless of the cause) is lacking at the time of this writing, although reports exist of various agents, administered either systemically or directly into the bladder, that have been successful in treating HC. For premenopausal women receiving cancer treatments that result in a prolonged and potentially severe period of thrombocytopenia (e.g., hematopoietic stem cell transplantation), the cessation of menses is desirable. Undoubtedly, hormonal agents (e.g., leuprolide) have been very effective in preventing normal menstrual bleeding in such patient populations and are considered an effective clinical practice, particularly in the hematopoietic stem cell transplantation population. However, this bleeding prevention intervention has not been systematically evaluated with sufficient evidence for it to be in the recommended for practice PEP category.

Thrombopoiesis-stimulating agents (or platelet growth factors) such as rhIL-11 held much clinical hope for reducing treatment-associated thrombocytopenia. However, the clinical benefit, as well as safety and tolerability of these agents, still is being evaluated. The ongoing clinical investigation of agents that stimulate megakaryocytopoiesis may provide sufficient evidence to support the safe and efficacious use of these agents, but they cannot be recommended for practice at this time. Likewise, the hemostatic effects of rFVIIa and its potential use in the prevention and management of bleeding in patients with cancer also is being explored.

Many interventions to prevent and manage bleeding come from expert opinion and are commonly employed in practice. And indeed, oncology nurses have a pivotal role in the prevention and management of bleeding, beginning with education directed at self-care and prevention of injury for patients expected to experience thrombocytopenia. Knowledge regarding these evidence-based guidelines should help nurses in the prevention and management of bleeding and assist in the delivery of optimally safe and high-quality care for patients with cancer.

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## Put Evidence Into Practice

For more information about evidence-based interventions for the prevention of bleeding, including the Putting Evidence Into Practice (PEP) resources, definitions, evidence tables, and a complete list of references, visit [www.ons.org/outcomes/volume3/bleeding.shtml](http://www.ons.org/outcomes/volume3/bleeding.shtml). PEP resources for several other nursing-sensitive patient outcomes are available at [www.ons.org/outcomes/topics.shtml](http://www.ons.org/outcomes/topics.shtml).

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