Nursing Considerations of Bevacizumab Use in Multiple Tumor Types

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Purpose/Objectives: To update information concerning the antiangiogenic agent bevacizumab, discuss side effects, and provide information on nursing management of the side effects.

Data Sources: Published articles, abstracts, and research data.

Data Synthesis: In clinical trials, the addition of bevacizumab to standard chemotherapy increased survival in patients with metastatic colorectal cancer and advanced non-small cell lung cancer and increased progression-free survival in patients with metastatic breast cancer. Bevacizumab also is being evaluated in combination with other targeted agents in various tumor types. Commonly reported side effects associated with bevacizumab include hypertension, proteinuria, and minor bleeding.

Conclusions: The value of bevacizumab in treating metastatic colorectal cancer has long been established. Clinical trial data have demonstrated the benefit of using bevacizumab in combination with standard chemotherapy in the treatment of non-small cell lung cancer and metastatic breast cancer. Because of bevacizumab's expanding role in cancer treatment, nurses need to know how to use it, be aware of possible side effects, and anticipate interventions.

Implications for Nursing: Nurses play an important role in the identification and management of adverse events associated with bevacizumab.

Key Points . . .

- Cytotoxic treatments for cancer are limited by their inability to selectively target tumor cells, producing well-characterized side effects, such as fatigue, hair loss, and bone marrow suppression. This limits the dosage given and thereby the overall effectiveness of treatment.
- Bevacizumab is the first approved targeted agent that specifically inhibits the vascular endothelial growth factor that plays a key role in angiogenesis, tumor growth, and metastases.
- Bevacizumab is the first antiangiogenic agent to consistently increase overall or progression-free survival in different tumor types, including metastatic colorectal cancer, advanced non-small cell lung cancer, and metastatic breast cancer.
- Oncology nurses play a vital role in the assessment and monitoring of common and rare side effects associated with bevacizumab therapy.

Patients with advanced stages of cancer have poor prognoses, and the goal of treatment is to prolong survival and improve quality of life. Chemotherapy has been the mainstay of treatment for advanced cancer for many years, but cytotoxic agents are limited by their inability to selectively target tumor cells. The nonspecificity often results in damage to healthy cells and produces well-characterized side effects, such as fatigue, hair loss, and bone marrow suppression. The nonspecificity of chemotherapy also can limit the dosages that can be given and, therefore, the effectiveness of treatment. More effective and better-tolerated cancer therapies are needed. New therapeutic agents that act directly on tumor cells or the cells supporting tumor growth are referred to as targeted therapies. The improved specificity of targeted agents means they are less likely to affect healthy cells, which should result in fewer side effects.

An improved understanding of the multistep process in cancer development has led to the identification of various potential therapeutic targets. Angiogenesis, the formation of new blood vessels, is a key target in tumor growth and metastatic spread. Proliferating tumor cells, similar to normal cells, must be supplied by blood vessels to provide vital nutrients and oxygen required for growth. Small tumors can grow to 1–2 mm by absorbing nutrients and oxygen through simple diffusion, but a vascular blood supply is required for further growth (Ferrara, 2004). A new blood supply normally is recruited from neighboring mature vasculature, which forms new blood vessels that grow toward and eventually into the tumor. The transition of a small avascular tumor to a large vascularized tumor with increased growth potential is known as an "angiogenic switch." The angiogenic switch is triggered by an increase in proangiogenic factors, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor, and transforming growth factor-alpha, and a decrease in antiangiogenic factors, including angiostatin, endostatin, and thrombospondin (Ferrara & Kerbel, 2005), as seen in Figure 1.

VEGF, also known as VEGF-A, has emerged as a key angiogenic factor involved in regulating the angiogenic switch. VEGF is a ligand that has numerous roles in angiogenesis. For example, it directly increases the permeability of blood vessels that may contribute to angiogenesis and tumor growth. In addition, VEGF promotes angiogenesis by binding to two receptors, VEGFR-1 (Flt-1) and VEGFR-2 (Flk-1/KDR). The receptors are found predominantly on the surface of endothelial

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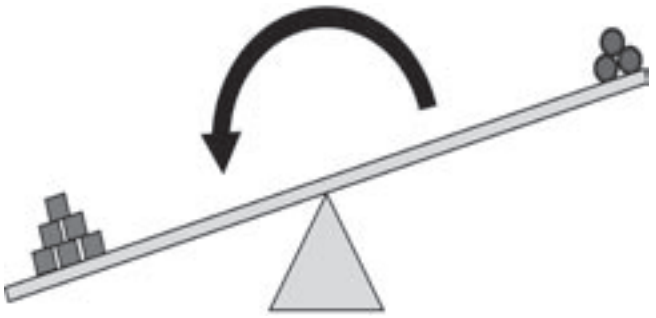
Digital Object Identifier: 10.1188/07.ONF.693-701



■ = Proangiogenic factors (e.g., vascular endothelial growth factor (VEGF), basic fibroblast growth factor, transforming growth factor-α)

● = Antiangiogenic factors (e.g., endostatin, angiostatin, thrombospondin-1)

Note. The mechanism controlling angiogenesis is referred to as the angiogenic switch. The balance between pro- and antiangiogenic factors is shifted. Increases in the level of proangiogenic factors such as VEGF can activate the switch, leading to the growth of new blood vessels.

Figure 1. The Angiogenic Switch

cells that form the lining of blood vessels (Gerber & Ferrara, 2005). Binding of VEGF to its receptors activates intracellular signal transduction pathways, which promote endothelial cell proliferation and survival, resulting in new blood vessel formation. The new vasculature not only allows the primary tumor to grow, but also provides the opportunity for tumor cells to access the circulation, enabling metastatic spread.

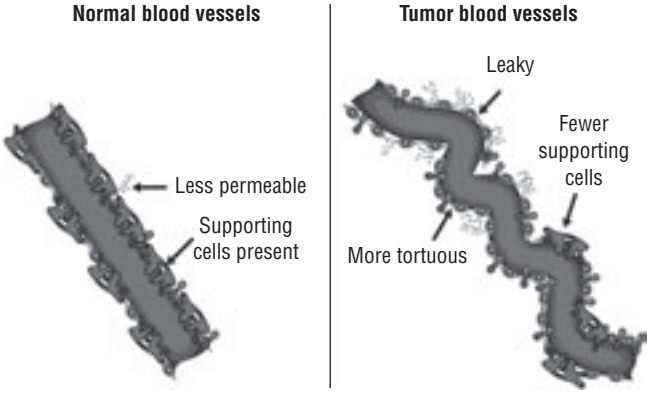
Many tumors overexpress VEGF, including cancers of the colon, lung, breast, and kidney. Increased expression has been shown to correlate with high tumor vascularity, invasiveness, metastasis, increased risk of disease recurrence, and decreased survival (Ferrara & Davis-Smyth, 1997). Therefore, the pivotal role of VEGF in tumor growth and metastasis has provided the rationale for targeting the molecule in cancer therapy.

A number of strategies have been developed to target VEGF. The most progress has been made with monoclonal antibodies and tyrosine kinase inhibitors. Monoclonal antibodies target the VEGF ligand, blocking VEGF from binding to its receptor, whereas tyrosine kinase inhibitors block the receptor(s), preventing intracellular signaling. Bevacizumab (Avastin®, Genentech BioOncology, Inc.), a humanized monoclonal antibody directed against VEGF, is the first antiangiogenic agent to be approved as an anticancer therapy. In 2004, the U.S. Food and Drug Administration (FDA) approved bevacizumab in combination with IV 5-fluorouracil (5-FU)–based chemotherapy for patients with previously untreated metastatic colorectal cancer, making a significant impact on the treatment of the disease. Approval of the agent was based primarily on data demonstrating that patients treated with bevacizumab plus irinotecan, 5-FU, and leucovorin (LV) chemotherapy (IFL) survived approximately five months longer compared with patients treated with chemotherapy alone (Hurwitz et al., 2004). Bevacizumab also has been approved as a second-line treatment for patients with metastatic colorectal cancer.

The Mechanisms of Action of Bevacizumab

To understand how coadministration of bevacizumab with chemotherapy can enhance the efficacy of standard treatments, healthcare professionals must differentiate between normal vasculature and tumor vasculature (see Figure 2). Tumor vasculature shows striking structural and functional differences compared with its normal, healthy counterpart. During tumor angiogenesis, the imbalance between pro- and antiangiogenic factors results in rapid growth of blood vessels (Jain, 2005). The resulting tumor vasculature is dilated and irregularly shaped and resembles immature blood vessels. The structural abnormalities contribute to irregular tumor blood flow and increased interstitial fluid pressure, which, in turn, reduce chemotherapy delivery to the tumor, limiting its effectiveness (Jain). Bevacizumab activity is not affected appreciably by increased interstitial fluid pressure around the tumor because it does not need to reach or penetrate tumor tissue itself, only the immediate vascular environment. However, bevacizumab may enhance the effect of chemotherapy by "normalizing" or pruning inefficient and immature blood vessels. This creates improved conditions for chemotherapy accessibility and greater penetration into the tumor—resulting in improved clinical outcomes (Hu et al., 2002; Sweeney et al., 2001; Wildiers et al., 2003).

Bevacizumab also has been shown to have direct tumor antivascular effects because it causes regression of existing microvessels and inhibits the neovascularization necessary for the growth of tumors beyond 2 mm. Preclinical studies showed that anti-VEGF monoclonal antibodies reduced tumor vessel diameter and made blood vessels less tortuous in various animal models (Yuan et al., 1996). Clinical studies confirmed the direct antivascular activity in human cancer (Willett et al., 2004). A single infusion of bevacizumab in patients with rectal carcinoma decreased volume of blood flow, microvessel density, and interstitial fluid pressure and normalized tumor vasculature.



Note. Tumor vasculature shows striking structural and functional differences compared with its normal healthy counterpart. Tumor vasculature is characterized by high permeability, irregular shapes, and an insufficient number of supporting cells. These structural abnormalities contribute to irregular tumor blood flow and increased interstitial fluid pressure, reducing delivery of chemotherapy into the tumor.

Figure 2. Normal and Tumor Vasculature

By preventing tumor growth and neovascularization, bevacizumab exerts a primarily cytostatic effect. This may serve patients in terms of overall survival and progression-free survival rather than actual tumor shrinkage. Importantly, the response-independent survival benefit was observed in a retrospective, exploratory analysis in patients with metastatic colorectal cancer (Mass, Sarkar, Holden, & Hurwitz, 2005). Mass et al. showed that patients who did not respond to bevacizumab treatment, as measured with the Response Evaluation Criteria in Solid Tumors, were nevertheless able to derive clinical benefit in terms of progression-free survival and overall survival. The data suggest that discontinuing bevacizumab in patients who do not have an objective tumor response may compromise the clinical benefit with respect to overall survival.

Clinical Trial Update

Following the pivotal bevacizumab phase III trial in patients with metastatic colorectal cancer, more trials have evaluated bevacizumab not only in the treatment of metastatic colorectal cancer, but also in other tumor types. The feasibility of the use of bevacizumab has been explored in combination with standard chemotherapy regimens, as well as with other modalities with different mechanisms of action such as other targeted agents. Efficacy and safety data of recent phase III clinical trials and other key studies in metastatic colorectal cancer, advanced non-small cell lung cancer (NSCLC), and metastatic breast cancer are summarized in Table 1.

Bevacizumab in Metastatic Colorectal Cancer

Bevacizumab is approved in combination with 5-FU–based therapy as first-line therapy for metastatic colorectal cancer and now is the standard of care. It is used most commonly in combination with infusional 5-FU–based regimens such as FOLFOX (5-FU/LV plus oxaliplatin) (Kozloff et al., 2006), which are more effective than bolus 5-FU–based regimens such as IFL (Goldberg et al., 2004).

The Eastern Cooperative Oncology Group (ECOG) randomized phase III trial assessed the clinical benefit of FOLFOX4 plus bevacizumab (10mg/kg every 14 days) in 579 patients with previously treated metastatic colorectal cancer (Giantonio et al., 2005). The addition of bevacizumab significantly increased overall survival (12.9 versus 10.8 months), progression-free survival (7.2 versus 4.8 months), and response rate (21.8% versus 9.2%) compared with FOLFOX alone (see Table 1).

Treatment options are limited for patients who have relapsed on irinotecan- or oxaliplatin-based chemotherapy; clinical studies have shown that bevacizumab plus 5-FU/LV is a viable option for such patients (Hurwitz et al., 2005; Kabbinavar et al., 2005). Another approach that may have potential for previously treated patients is the simultaneous inhibition of pathways involved in tumor growth and development, using targeted agents with different mechanisms of action. The BOND-2 clinical trial assessed the feasibility of dual pathway inhibition with two such targeted agents, bevacizumab and cetuximab, in patients with previously treated metastatic colorectal cancer (Saltz et al., 2005). Cetuximab, a recombinant monoclonal antibody that targets another protein implicated in cancer, the human epidermal growth factor receptor, is approved for use in patients with previously treated metastatic colorectal cancer either in combination with irinotecan or as monotherapy if patients are unable to tolerate irinotecan. Combination therapy with targeted agents may be a valid option for patients who have relapsed on chemotherapy.

Bevacizumab in Other Solid Tumor Types

The efficacy of bevacizumab also has been evaluated in a number of other solid tumors, including NSCLC and metastatic breast cancer. An Eastern Cooperative Oncology Group randomized phase III trial (E4599) demonstrated that the addition of bevacizumab (15 mg/kg every three weeks) to paclitaxel/carboplatin (the current standard of care) increased response rate (27.2% versus 10.0%), progression-free survival (6.4 months versus 4.5 months), and overall survival (12.5 months versus 10.2 months) compared with paclitaxel/carboplatin alone in patients with previously untreated advanced non-squamous NSCLC (Sandler et al., 2005). Based on the data, bevacizumab in combination with carboplatin/paclitaxel is now the new ECOG reference standard for patients with previously untreated advanced NSCLC (Sandler et al.).

An ECOG randomized phase III trial also demonstrated that the addition of bevacizumab (10 mg/kg every two weeks) to paclitaxel significantly improved response rates (29.9% versus 13.8%) and progression-free survival (11.40 versus 6.11 months) compared with paclitaxel alone in patients with previously untreated metastatic breast cancer (Miller et al., 2005b). Interim results suggest that bevacizumab also may increase overall survival, although the findings need to be confirmed.

In addition, bevacizumab has been assessed in renal cell, ovarian, pancreatic, hepatocellular, and gastric cancers. The studies examined bevacizumab as monotherapy or in combination with standard therapy or with other targeted agents. Preliminary findings are encouraging. Ongoing and planned studies will provide further information on the efficacy of bevacizumab in such tumor types.

Dose

The recommended dose of bevacizumab, in combination with IV 5-FU–based chemotherapy, as first-line therapy for patients with metastatic colorectal cancer is 5 mg/kg given once every 14 days as an IV infusion until disease progression is detected (Genentech, Inc., 2005). Bevacizumab does not appear to display a consistent dose-response relationship. Thus, the aim for antiangiogenic agents, such as bevacizumab, is to achieve an optimal biologically active dose rather than to find the maximum tolerated dose, which is needed for traditional chemotherapy agents. Indeed, antiangiogenic agents may need long-term, continuous administration to reach maximum efficacy (Bergsland & Dickler, 2004). Dosage levels employed in phase II trials of bevacizumab in patients with various advanced, solid tumors have ranged from 3–20 mg/kg administered every two or three weeks. However, in all studies outside first-line metastatic colorectal cancer, the dose that has been demonstrated to be efficacious is 5 mg/kg per week equivalent. Therefore, if bevacizumab is given every two weeks, the dose is 10 mg/kg; if bevacizumab is given every three weeks, the dose is 15 mg/kg (Genentech, Inc.; Giantonio et al., 2005; Sandler et al., 2005). Further studies may be required to define the optimal bevacizumab dose in various tumor types and settings.

Table 1. Ongoing Bevacizumab (BV) Clinical Trials in Advanced or Metastatic Cancers

Tumor Type (Trial Name)	Authors	Regimen	Overall Survival (Months)	Progression-Free Survival (PFS) or Time to Progression (TTP) (Months)	Complete Response Plus Partial Response
Colorectal cancer (TREE-2)	Hochster et al., 2006	BV + mFOLFOX6	26.0 (19.2)[a]	TTP: 9.9 (8.4)[a]	53% (43%)[a]
		BV + bFOL	20.7 (17.9)[a]	TTP: 8.3 (6.9)[a]	41% (22%)[a]
		BV + CapeOx	27.0 (17.2)[a]	TTP: 10.3 (5.9)[a]	48% (35%)[a]
Colorectal cancer	Bendell et al., 2006	BV + CapeOx	Not applicable	PFS: 10.7	53%
Colorectal cancer	Kopetz et al., 2006	BV + FOLFIRI	Not applicable	PFS: 12.5	74%
Colorectal cancer (E3200)	Giantonio et al., 2005	BV + FOLFOX4 vs FOLFOX4	12.9 versus 10.8	PFS: 7.2 versus 4.8	21.8% versus 9.2%
Colorectal cancer (BOND-2)	Saltz et al., 2005, 2006	BV + cetuximab versus historical control (cetuximab)	Not applicable	TTP: 7.9 versus 4.0	37% versus 23%
		BV + cetuximab/irinotecan versus historical control (cetuximab/irinotecan)	Not applicable	TTP: 5.6 versus 1.5	20% versus 11%
Non-small cell lung cancer (E4599)	Sandler et al., 2005	BV + paclitaxel/carboplatin versus paclitaxel/carboplatin	12.5 versus 10.2	PFS: 6.4 versus 4.5	27.2% versus 10.0%
Breast cancer (E2100)	Miller et al., 2005b	BV + paclitaxel versus paclitaxel	28.4 versus 25.2	PFS:11.4 versus 6.11	29.9% versus 13.8%

[a] These findings were compared with data from TREE1, a comparison of the same chemotherapy regimens without BV.

Note. bFOL—oxaliplatin 85 mg/m^2 every two weeks, leucovorin 20 mg/m^2 IV bolus, and 5-FU 500 mg/m^2 IV bolus on days 1, 8, and 15 every four weeks; CapeOx—oxaliplatin 130 mg/m^2 and capecitabine 1,000 mg/m^2 on days 1–14 every three weeks; cetuximab and cetuximab + irinotecan—cetuximab 400 mg/m^2 loading dose, then 250 mg/m^2 weekly, irinotecan at same dose and schedule as last given prior to study entry; FOLFIRI—irinotecan 180 mg/m^2 on day 1, leucovorin 400 mg/m^2 on day 1, 5-FU 400 mg/m^2 IV bolus on day 1 followed by 5-FU 2,400–3,000 mg/m^2 over 46 hours every two weeks; FOLFOX4—oxaliplatin 85 mg/m^2 on day 1, leucovorin 200 mg/m^2 on days 1 and 2, and 5-fluorouracil (5-FU) 400 mg/m^2 IV bolus followed by 600 mg/m^2 IV over 22 hours on days 1 and 2 every two weeks; mFOLFOX6—oxaliplatin 85 mg/m^2 on day 1, leucovorin 350 mg/m^2 on day 1; 5-FU 400 mg/m^2 IV bolus on day 1 followed by 2,400 mg/m^2 via IV over 46 hours every two weeks; paclitaxel—90 mg/m^2 on days 1, 8, and 15 every four weeks; paclitaxel/carboplatin—paclitaxel 200 mg/m^2, carboplatin area under the curve = 6 on day 1 every three weeks.

Note. According to Response Evaluation Criteria in Solid Tumors, complete response is defined as disappearance of all detectable tumor, partial response is defined as at least 30% tumor shrinkage, progressive disease is defined as 20% increase in tumor growth or appearance of new tumors, and stable disease is defined as neither sufficient tumor shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease.

Currently, no reliable marker of bevacizumab activity has been identified. One obvious marker is VEGF; however, a relationship between plasma VEGF concentration and bevacizumab's survival benefit was not observed in patients with metastatic colorectal cancer (Holden, Ryan, Kearns, Holmgren, & Hurwitz, 2005). Elevated VEGF levels are prognostic, but they have not been demonstrated to be predictive of response to bevacizumab-containing therapy; therefore, the search for a reliable marker continues.

Adverse Events Associated With Bevacizumab

Nurses have a significant role in the identification and management of side effects associated with cancer therapy (Rosiak & Sadowski, 2005). In theory, inhibiting tumor angiogenesis with targeted anti-VEGF therapy should result in less nonspecific toxicity compared with cytotoxic agents (Fernando & Hurwitz, 2004). Bevacizumab has not been associated with the side effects typically associated with chemotherapy, such as fatigue, hair loss, and bone marrow suppression, although the side effects still occur when bevacizumab is used in combination with chemotherapy. Although considered to have a positive risk-to-benefit ratio, treatment with bevacizumab is associated with adverse events that may or may not be related to its mechanisms of action.

Bevacizumab has been generally well tolerated in all of the trials discussed earlier. The adverse events observed with bevacizumab can be divided into commonly observed side effects, including hypertension, proteinuria, and minor bleeding, and serious but rare adverse events, such as hemoptysis, bowel perforations, arterial thromboembolic events, and wound-healing complications.

Hypertension

Hypertension was reported in all studies involving bevacizumab. The prescribing information for bevacizumab indicates the that incidence of hypertension (defined as systolic blood pressure > 150 mmHg and diastolic pressure > 100 mmHg) among patients with metastatic colorectal cancer receiving bevacizumab plus IFL was 60%, compared with 43% observed in patients not receiving bevacizumab (Genentech, Inc., 2005). Severe hypertension (defined as systolic blood pressure > 200 mmHg and diastolic pressure > 110 mmHg) was nearly 7% in bevacizumab-treated patients, compared with 2% in the placebo group (Genentech, Inc.). The data include all patients with either a systolic or diastolic reading greater than the stated values on one or more occasions. In the Hurwitz et al. (2004) phase III trial, National Cancer Institute Common Toxicity Criteria version 2.0 were used to grade side effects. The overall incidence of hypertension (of any grade) was 22.4% in the be-

vacizumab plus IFL group, versus 8.3% in the placebo group; the incidence of grade 3 hypertension (requiring therapy or more intensive therapy than previously used) was 11% versus 8.3%, respectively. No hypertensive crises (grade 4 hypertension) were reported in either group.

Proteinuria

An increase in the incidence and severity of proteinuria has been observed in patients receiving bevacizumab, although it was mainly mild to moderate in severity (Kabbinavar et al., 2003; Yang et al., 2003). In addition, the majority of patients who developed new or increased proteinuria were asymptomatic (Yang et al.). Interestingly, reported data from the pivotal phase III trial in colorectal cancer suggested that severe proteinuria is not increased in patients receiving bevacizumab plus standard chemotherapy (Hurwitz et al., 2004).

Bleeding

Two types of bleeding have been identified during bevacizumab therapy (Genentech, Inc., 2005; Johnson et al., 2004). The first, and more commonly observed, was minor bleeding such as epistaxis. The second, more serious type of bleeding was rare but sometimes resulted in life-threatening, hemorrhagic events and occurred primarily in patients with NSCLC. Five of 420 patients (1.2%) with NSCLC reported serious hemorrhagic events, the majority presenting as hemoptysis (Sandler et al., 2005). The events occurred despite patient selection for nonsquamous cell histology, which is thought to have a lower risk for pulmonary hemorrhagic events based on a previous trial (Johnson et al., 2004). However, no serious hemorrhagic events were seen in the metastatic colorectal cancer studies.

Bowel Perforation

Rare cases of bowel perforations first were reported in 1.5% of patients being treated with bevacizumab for metastatic colorectal cancer (Hurwitz et al., 2004), consistent with findings later reported by Giantonio et al. (2005) and the BRiTE study (Kozloff et al., 2006). In the BRiTE study, an interim analysis showed that specific baseline characteristics (primary tumor intact, recent prior history of sigmoidoscopy or colonoscopy, or prior adjuvant radiotherapy) appeared to result in a slightly higher incidence of bowel perforation (Sugrue et al., 2006). In addition, most events occurred early (52% of patients reported bowel perforations in the first three months of treatment). The findings are supported by preliminary results from the first BEAT study (an international observational study that enrolled 1,927 patients in 41 countries), which also showed that patients without resection of the primary tumor may have a small increased risk of bowel perforation and gastrointestinal bleeding (Kretzschmar et al., 2006).

Arterial Thrombotic Events

An analysis of five randomized bevacizumab clinical trials in advanced or metastatic cancers (metastatic colorectal cancer, advanced NSCLC, and metastatic breast cancer) noted that arterial thrombotic events were increased in patients receiving bevacizumab plus chemotherapy (3.8%), compared with those receiving chemotherapy alone (1.7%) (hazard ratio = 1.99; $p = 0.03$) (Skillings et al., 2005). Arterial thromobotic events were either cerebro- or cardiovascular events such as stroke, transient ischemic attack, myocardial infarction, angina, and arterial thrombosis. Risk factors included a prior history of arterial thromobotic events and age of 65 years or more (Skillings et al.). Bevacizumab provides a consistent survival benefit in patients with metastatic colorectal cancer in all prespecified subgroups, including those with an increased risk of arterial thromobotic events. Importantly, venous thrombosis was not increased by the use of bevacizumab (Novotny et al., 2004).

Wound-Healing Complications

A potential difficulty associated with the use of an antiangiogenic agent such as bevacizumab is the risk of delayed wound healing in patients undergoing surgery. Findings from the first BEAT study showed that minor surgery such as implantation of a venous access device does not result in increased risk of wound-healing complications (Berry et al., 2006a).

However, analysis of postoperative wound-healing complications among patients with metastatic colorectal cancer who underwent major surgery suggests that bevacizumab therapy may be associated with a slightly increased risk of wound healing in patients undergoing surgical procedures during the course of treatment (Scappaticci et al., 2005). A safe interval between termination of bevacizumab and subsequent surgery has not yet been determined, but because of the potential for impaired wound healing, bevacizumab therapy should be suspended for several weeks before elective surgery (the recommendation is based on bevacizumab's half-life of 21 days) (Genentech, Inc., 2005). Similarly, the appropriate interval between major surgery and initiation of bevacizumab therapy has not been determined; however, bevacizumab should not be initiated for at least 28 days and until the wound is fully healed (Genentech, Inc.). No serious postoperative wound healing problems were observed in patients who underwent surgery 28–60 days prior to starting bevacizumab therapy (Scappaticci et al., 2005).

Because the optimal use of bevacizumab requires prolonged periods of administration, the incidence of toxicities requires further study. The overall safety profile of bevacizumab in patients with metastatic colorectal cancer is being evaluated in the BRiTE and first BEAT observational studies (Berry et al., 2006b; Hedrick et al., 2006). Interim analyses from the studies showed that the safety profile of bevacizumab in combination with various chemotherapies used in previously untreated patients appears to be consistent with that observed in the large phase III trials (Berry et al., 2006b; Hedrick et al.; Hurwitz et al., 2004). Data from the trials will help elucidate the safety profile and efficacy of bevacizumab in combination with different chemotherapy regimens.

Nursing Management of Bevacizumab-Related Adverse Events

The effective management of therapy-related adverse events is important for the well-being of patients and their families. This is especially relevant with respect to biologic agents because any information nurses obtain from patients can be significant in defining the toxicity profile of the agents (Reiger, 2001). Nurses also play a crucial role in patient education, encouraging more accurate reporting of adverse events and, therefore, better management. Advanced practice nurses also may have prescriptive authority to select and prescribe indicated treatments for commonly occurring bevacizumab-related events, such as hypertension. The following section has recommendations for

the management of events related to the use of bevacizumab. The recommendations also are summarized in Figure 3.

Hypertension

Prompt nursing interventions and a plan for care are needed to manage patients with hypertension. Nurses measure blood pressure before treatment initiation and every two or three weeks during bevacizumab treatment; patients who develop hypertension may require blood pressure monitoring at more frequent intervals (Genentech, Inc., 2005). For management of hypertension, standard oral antihypertensive agents such as calcium-channel blockers, angiotensin-converting-enzyme inhibitors, and diuretics may be prescribed (Hurwitz et al., 2004). Hypertension treatment may need to be adjusted to maintain normal blood pressure in patients already taking antihypertensives. Bevacizumab should be suspended temporarily for patients with severe hypertension (> 200/110 mmHg) that is not controlled with antihypertensives and should be discontinued in patients with hypertensive crisis (Genentech, Inc.), with continued regular blood pressure monitoring.

Proteinuria

Patients receiving bevacizumab should undergo serial monitoring for protein levels prior to and during bevacizumab therapy. Regular assessment of proteinuria is required because hydration and nutrition affect urine density and volume. In addition, comorbidities that can contribute to proteinuria, such as hypertension and diabetes, should be considered. Bevacizumab should be discontinued permanently in patients with nephrotic syndrome (renal disease that is characterized by very high levels of protein in urine, edema, high cholesterol levels, hypoalbuminemia, and hypercoagulability).

Although proteinuria traditionally is assessed by urinary dipstick or 24-hour urinalysis, current clinical trials are em-

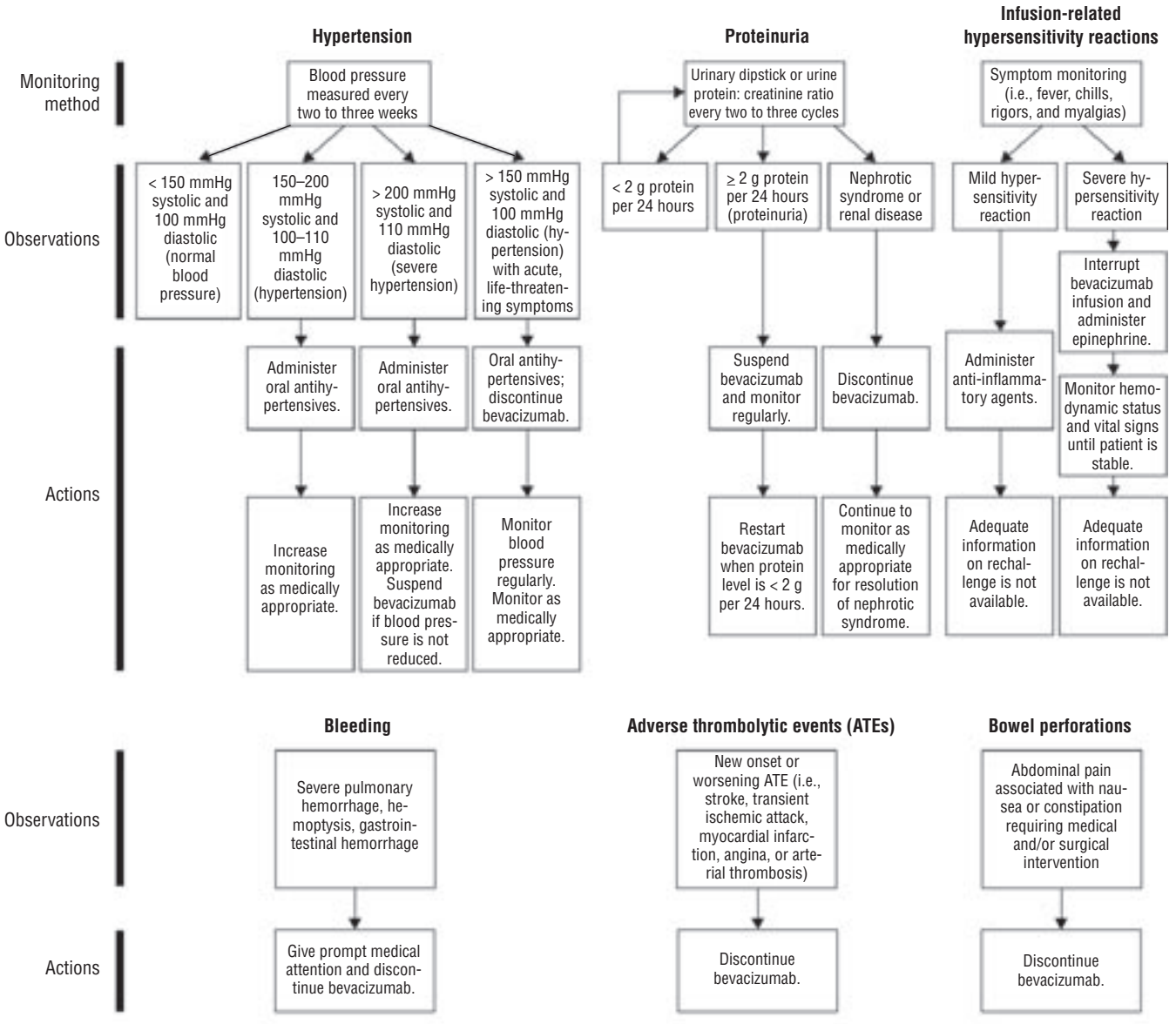


Figure 3. Serious Adverse Events

Note. Based on information from Genentech, Inc., 2005; Gobel, 2005; Hurwitz et al., 2004.

ploying urine protein: creatinine (UPC) ratio. UPC ratio has been correlated with 24-hour urinalysis results in patients with renal disease (Carroll & Temte, 2000; Ralston et al., 1988; Rodby et al., 1995; Saudan, Brown, Farrell, & Shaw, 1997).

Bleeding

Nurses must educate patients about the management of minor bleeding (e.g., for epistaxis, pressure should be applied to the bridge of the nose) and the importance of reporting any bleeding events (Wilkes, 2005). Events such as epistaxis may not need treatment if they last less than five minutes and resolve spontaneously. Low-dose aspirin (≤ 325 mg per day) in combination with bevacizumab does not further increase the risk of bleeding events in patients with metastatic colorectal cancer (Hambleton et al., 2005). If required, low-dose aspirin or nonsteroidal anti-inflammatory medications may be given to patients, except those with NSCLC or with a history of bleeding diathesis (Franson & Lapka, 2005). More serious patterns of hemorrhage such as pulmonary (e.g., hemoptysis) and gastrointestinal hemorrhage require prompt medical attention and discontinuation of bevacizumab (Genentech, Inc., 2005). Patients with a disposition for bleeding or with central nervous system metastases should not receive bevacizumab therapy.

Thrombosis

Symptoms of thrombosis include any new swelling or changes in the legs or thighs, pain in the abdomen, rapid heartbeat, chest pain or pressure, and increased headaches or visual disturbances, lightheadedness, or dizziness (Wilkes, 2005). For patients who experience new onset of severe arterial thromobotic events during treatment, bevacizumab should be discontinued permanently (Genentech, Inc., 2005). The safety of resumption of bevacizumab after resolution of an arterial thrombotic event has not been evaluated. Low-dose aspirin is used as standard therapy for primary and secondary prophylaxis of arterial thromobotic events in high-risk patients. In one analysis, concomitant use of low-dose aspirin and bevacizumab did not further increase the risk of bleeding events, but the potential effect of concomitant low-dose aspirin use on the incidence of arterial thromboembolic events in patients treated with bevacizumab requires additional study (Hambleton et al., 2005). Patients with unstable angina, coagulopathy, significant peripheral vascular disease, or a history of stroke or myocardial infarction within six months should not receive bevacizumab (Genentech, Inc., 2005).

Bowel Perforation

Patients need to be informed of rare reports of bowel perforations associated with bevacizumab therapy. Factors that may be associated with bowel perforations include a history of acute diverticulitis, abscess, obstruction, or abdominal or pelvic radiation; tumor at the site of perforation; abdominal carcinomatosis; or unresected primary tumor, although no clear factors for increased risk have been identified (Kretzschmar et al., 2006; Sugrue et al., 2006). Patients should be instructed to report any abdominal pain associated with nausea or constipation (Wilkes, 2005). Bevacizumab should be discontinued permanently in patients who develop bowel perforation (Genentech, Inc., 2005).

Infusion Reactions

Bevacizumab initially is infused over 90 minutes. Subsequent infusions can be reduced to 60 minutes, then 30 minutes if no infusion-related reactions occur (Genentech, Inc., 2005; Miller et al., 2005a). No significant infusion-related symptoms were noted in trials with bevacizumab, and premedication is not required. A single institution's practice of using 30-minute infusions for all doses of bevacizumab (5 mg/kg) resulted in no hypersensitivity reactions in 464 patients with metastatic colorectal cancer (Saltz et al., 2006). This suggests that bevacizumab can be administered safely as a 30-minute infusion without the need for the initial 90- and 60-minute infusions, which may be more convenient for patients and hospital staff.

Although bevacizumab is a humanized monoclonal antibody and not a chimeric antibody, nurses should monitor patients for hypersensitivity reactions, including fever, chills, rigors, and myalgias, during bevacizumab infusion (Franson & Lapka, 2005). If an infusion reaction occurs, the infusion should be interrupted and standard therapy administered as for other biologic agents. Patients with mild infusion reactions may benefit from oral prednisone or dexamethasone (Gobel, 2005). Epinephrine is standard therapy for a severe hypersensitivity reaction. Although no standard dose of epinephrine is recommended, a suggested protocol is 0.3–0.5 ml subcutaneously of a 1:1000 aqueous epinephrine solution diluted in 10 ml of normal saline. The dose can be infused over 5–10 minutes, resulting in a total dose of 10 μg (Gobel). Hemodynamic monitoring should be observed closely in patients with infusion reactions. Vital signs should be taken every two to five minutes until a patient is stable and every 15 minutes thereafter (Gobel).

Conclusion

The clinical development of bevacizumab has come a long way since the release of phase III data in patients with untreated metastatic colorectal cancer. Two years later, phase III trials of bevacizumab in combination with standard chemotherapy have demonstrated increased overall survival or progression-free survival in patients with metastatic colorectal cancer, advanced NSCLC, and metastatic breast cancer. Bevacizumab also is being evaluated in adjuvant trials as a potential therapy in colorectal, lung, and breast cancer and in advanced stages of several other cancers. The value of bevacizumab in treating cancer will be better elucidated as clinical trial data become available and are presented at future meetings. Given the expanding role of bevacizumab in cancer treatment, nurses need to know how to use bevacizumab, be aware of possible side effects, and anticipate nursing interventions.

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