Catheter-Related Thrombosis: Risks, Diagnosis, and Management

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Key Words

Thrombosis, central venous catheter, deep vein thrombosis, pulmonary embolism, anticoagulation

Abstract

Symptomatic thromboembolic complications of central venous catheters (CVCs) occur in 5% or less of general oncology patients. Asymptomatic CVC-related thrombi are more common, but their clinical significance is unclear. Thrombotic risk may be increased by primary thrombophilic disorders, especially the factor V G1691A (Leiden) mutation, thrombogenic catheter material, larger catheter diameter and greater number of lumens, catheter tip malposition, left-sided placement, percutaneous or multiple insertion attempts, a previous CVC or preexisting venous obstruction, prothrombotic therapeutic agents, catheter-associated infections, and fibrinous catheter lumen occlusion. Three recent randomized, prospective, placebo-controlled trials observed no benefit of routine low-dose warfarin or low-molecular-weight heparin in preventing catheter-associated thrombosis. Nevertheless, thromboprophylaxis may be appropriate and safe for selected high-risk patients. Duplex ultrasound can accurately detect CVC-related thrombi involving the jugular, axillary, distal subclavian, and arm veins. Contrast venographic imaging is required for indeterminate duplex findings and to evaluate the deep central veins and pulmonary arteries. Therapeutic anticoagulation, with or without catheter removal, is indicated for patients with acute deep vein thrombosis (DVT) or pulmonary embolism who have no contraindications. Catheter removal alone, with close follow-up, may be sufficient when bleeding risk precludes safe anticoagulation. Approaches to managing catheter-associated thrombosis, including the use of thrombolytic agents, are guided by limited published experience and extrapolation from practices used for lower-extremity DVT. Prospective, randomized, controlled trials

are needed to identify the safest and most effective anticoagulant agents, treatment durations, and alternative venous access strategies for cancer patients who develop catheter-associated thrombosis. (*JNCCN* 2006;4:889–901)

Implanted and external semipermanent central venous catheters (CVCs) are essential for optimal management of complicated patients with solid tumors and hematologic malignancies. Their usefulness for blood sampling, infusions, and, in some cases, apheresis procedures is counterbalanced by the fact that these devices are nonbiologic foreign bodies that can activate coagulation locally and interact physiologically with hereditary and acquired hypercoagulable conditions to induce thrombosis.

Among the general population, roughly 9% of first venous thromboembolic events are causally associated with a CVC or transvenous pacemaker, and recent CVC placement increases the risk for upper-extremity deep vein thrombosis (DVT) by 5- to 7-fold.^{1,2} Spontaneous upper-extremity DVT is 2.6- to 8-fold more likely among patients with active cancer,^{3,4} and a CVC significantly augments that risk.^{4,5} The managing oncologist must be cognizant of this risk and that additional circumstances that further predispose to thrombosis may justify the use of prophylactic anticoagulation for selected patients. Moreover, because catheter-associated thromboembolic events are still relatively common among high-risk subgroups, the optimal approaches for diagnosis and management are important to understand.

Device-Related Incidence and Risk Factors

Central venous access devices that are designed for long-term use include surgically tunneled, externalized single or multiple lumen catheters, and fully implanted catheters that are connected to resealable diaphragm ports that are positioned under the skin of the chest or arm.

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Peripherally inserted central catheters (PICCs) are also commonly used for patients who require only temporary access (e.g., weeks as opposed to many months). Different models of each of these catheter types are manufactured with intraluminal pressure-sensitive valves that prevent passive blood reflux. Temporary or tunneled CVCs are also available with larger lumen diameters that accommodate the high flow rates necessary for leukapheresis (e.g., to collect peripheral blood stem cells) or other apheresis procedures. These double- or triple-lumen external devices are inserted into the internal jugular, subclavian, or femoral vein. Tunneled apheresis catheters that are used for stem cell collection are commonly retained throughout the course of hematopoietic stem cell transplant (HSCT), unless a complication necessitates removal.

PICCs

Thrombotic complications specifically associated with PICCs and implanted port systems have been characterized in retrospective and prospective cohort studies. Based on recent observations, occult PICC-related venous thrombosis is detected in 23% to 39% of cancer patients undergoing surveillance venography,^{6,7} whereas symptomatic thromboembolism (manifested by pain, swelling, or erythema) or thrombotic occlusion requiring catheter removal occurs in only 3.4% to 3.9% of patients.^{8,9} Most symptomatic events with PICCs occur within the first 2 weeks of placement and involve the cephalic or basilic arm veins rather than the central vessels. Higher thrombotic risk is associated with larger lumen diameter and infusion of chemotherapy.⁸

Central Port Catheters

Clinically overt upper-extremity thrombosis occurs in 0% to 9% of cancer patients with port catheters that are implanted in the chest.¹⁰⁻¹⁶ By comparison, thrombotic complications are more common in arm ports, with incidence rates ranging from 2% to 30%.^{10,11,14} As with PICCs, many of the events with arm ports involve the proximal arm veins rather than the central veins. Port-related DVT is predisposed by catheter tip malposition.¹²⁻¹⁴ Left-sided placement (compared with right) has been identified as a risk factor in some studies^{14,15} but not in others.^{13,16} One prospective randomized clinical trial found no differences in the rates of overall thrombosis with central (chest) ports connected to valved lumens compared with port catheters with open lumens (4% vs. 7.3%).¹⁶

External Tunneled Catheters

Long-term, tunneled, external CVCs induce thrombosis at rates similar to implanted chest port catheters; however, the reported incidence varies based on the study population and diagnostic criteria. In the early 1990s, approximately 9% of patients with hematologic malignancies undergoing HSCT developed symptomatic CVC-related thrombosis and up to 63% were found to have asymptomatic subclavian vein thrombosis on venographic surveillance.¹⁶⁻¹⁹ More recent prospective and retrospective studies that included only cancer patients observed symptomatic thrombosis in 4.7% to 10% of adults²⁰⁻²² and 2% to 2.5% of children with tunneled external CVCs.^{23,24} Incidence rates of asymptomatic clots ranged from 30% to 74%.^{25,26} As with implanted ports, tunneled catheters with closed (valved) lumens offer no added protection from thrombotic complications when compared with open-lumen catheters.¹⁷ One patient subgroup that appears to be at greater risk with external catheters than with implanted ports is children with acute lymphoblastic leukemia (ALL). A 3.9-fold higher rate of thrombosis was observed among 49 children with ALL and external CVCs compared with 236 children with implanted ports.²⁷

General Incidence and Technical Risk Factors

Recent prospective thromboprophylaxis trials that included patients with all types of catheters showed generally lower incidence rates of CVC-related thrombosis compared with earlier studies (see later discussion). This trend contradicts the higher annual percentages of venous or arterial thrombotic complications diagnosed among cancer patients in 2002 compared with 1995.²⁸ The reason for this discrepancy is not clear but may relate to avoidance or minimization of technical risk factors that predispose to CVC-associated thrombosis, including thrombogenic catheter material (e.g., polyethylene compared with polyurethane or silicone),²⁹ larger catheter diameter or greater number of catheter lumens,^{8,17,20,22,24} catheter tip malposition,^{12-14,20,21,30} percutaneous insertion techniques (compared with cut-down),³¹ left-sided placement,^{14,15,31,32} or two or more insertion attempts (compared with one; see Table 1).³³ A potential additional risk, at least in some adults with malignancies²² and children with ALL who receive asparaginase,³¹ but not in general medical or surgical patients,³⁴ is the insertion of the CVC in the subclavian vein compared with the internal jugular vein.

Table 1 Risk Factors Associated with Central Venous Catheter–Related Thromboembolism Among General Oncology Patients or Patient Subgroups**Technical**

Thrombogenic catheter material
 Larger catheter diameter or greater number of catheter lumens
 Catheter tip malposition
 Percutaneous insertion techniques (compared with cut-down)
 Two or more insertion attempts
 Prior CVC insertion
 Left-sided placement
 Subclavian vein insertion (compared with internal jugular)

Patient and Vascular

Catheter-associated infection
 Fibrinous catheter lumen occlusion
 Extrinsic vascular compression
 Factor V G1691A (Leiden) mutation (and possibly other thrombophilias)
 Prior venous thromboembolism
 Ovarian cancer

Treatment-Related

L-asparaginase (during induction therapy for acute lymphoblastic leukemia)
 Estrogen or progesterone agents
 Recombinant human erythropoietin (with chemotherapy and radiation for cervical cancer)
 Interleukin-2 (for melanoma or renal cell carcinoma)
 Granulocyte-macrophage colony-stimulating factor (during peripheral blood stem cell mobilization and collection)
 Thalidomide (in combination with corticosteroids or additional agents for myeloma)
 Heparin (in the setting of heparin-induced thrombocytopenia)

Patient and Treatment-Related Risks**Disease and Vascular Factors**

Cancer-related lower-extremity DVT and pulmonary embolism (PE) are strongly associated with specific malignant diagnoses, metastatic disease stage (compared with limited-stage disease), additional medical comorbidities, and active anticancer therapy.^{28,35,36} However, only a couple of potential disease-specific risk factors have been identified for CVC-related thrombosis. Two studies have reported statistically significant (5.6- and 4.8-fold) higher risks for catheter-related thrombosis in patients with ovarian cancer compared with other tumor types.^{14,33} However, only 14 patients with ovarian cancer were included in the retrospective study,¹⁴ and the more recent prospective trial³³ was confounded by the fact that the women with ovarian cancer had undergone more venipunctures and chemotherapy than other patient groups. Enlarged

cervical or mediastinal lymph nodes were associated with port-related thrombophlebitis in a study of patients with various solid tumors, suggesting that external vascular compression might be an independent risk factor.¹²

Prior CVC insertion was associated with a 3.8-fold higher risk for catheter-related thrombosis in a recent prospective trial.³³ This relationship may be explained by the fact that 14% to 40% of children and adults with a prior CVC have central vein thrombosis or stenosis on follow-up imaging studies.^{37–39} The significance of a personal history of DVT is unclear. A study of 252 patients, including 136 with malignancies, who underwent prospective weekly Doppler imaging, showed a 2-fold relative risk for catheter-related DVT among those with a prior history of venous thrombosis.⁴⁰ By comparison, no significant association was observed for venous thrombotic events, including

a 1.5% rate of symptomatic catheter-related DVT, among 416 patients with hematologic malignancies.⁴¹

Recent studies have identified close associations between catheter-related infections and CVC thrombosis in cancer patients. One prospective trial that used ultrasound surveillance every 4 days found that early detection of thrombosis was 86% sensitive and 97% specific for an associated catheter-related bacterial line colonization, exit site infection, or bacteremia (positive and negative predictive values were 92% and 93%, respectively).⁴² In turn, the risk for developing clinically overt catheter-associated thrombosis was 18-fold greater among patients who were previously diagnosed with a CVC-related infection compared with those without a line infection.⁴³ Septic thrombophlebitis is a serious complication of a catheter-related clot. In this regard, imaging with fluorine-18 fluorodeoxyglucose positron emission tomography can help in identifying deep vein septic thrombophlebitis in cancer patients with a CVC and recurrent bacteremia.⁴⁴

Thrombophilic Disorders in Children

Hereditary and acquired thrombophilic conditions may contribute to the risks for catheter-related DVT among children with certain malignancies or undergoing certain therapies. A prospective study of 140 children, including 16 with leukemia, neuroblastoma, or Hodgkin lymphoma, showed that the factor V G1691A (Leiden) mutation, protein C deficiency, and elevated lipoprotein (a) had significant associations with clinically symptomatic CVC-related thrombosis.⁴⁵ Two observational studies that included children with all types of hematologic malignancies and solid tumors also found frequent associations of symptomatic CVC-related thrombosis with heterozygous factor V Leiden mutation, elevated lipoprotein (a), or heterozygous prothrombin (factor II) G20210A mutation, with a high prevalence among children with ALL.^{46,47}

A prospective German trial of children with ALL who were treated on a regimen that included L-asparaginase during induction therapy showed a strong positive correlation between thrombosis in the upper extremity or cerebral vessels and the presence of a CVC.⁴⁸ Moreover, patients with 1 or more thrombophilic defects (mostly factor V or II mutations, elevated lipoprotein (a), and the TT 677 genotype of methylenetetrahydrofolate reductase [MTHFR]) had a significantly reduced thrombosis-free survival.⁴⁸ By

comparison, no thrombophilia-related risks were identified among children with ALL treated on a protocol that delayed the use of L-asparaginase until the intensification phase of treatment,⁴⁹ or in 2 prospective cohort studies of children with ALL who underwent routine surveillance imaging to detect an asymptomatic clot.^{50,51} Notably, these latter 2 trials were underpowered to observe a potential significant association. An additional case-control study that included 10 children with ALL and 5 with non-Hodgkin lymphoma found no association between CVC-related thrombosis and factor V Leiden mutation.⁵² Collectively, these data in children suggest that thrombophilic defects may play a role in CVC-related thrombosis in the context of additional treatment or disease-related prothrombotic risk factors.

Thrombophilic Disorders in Adults

Studies of various thrombophilic disorders in adults with malignancies have found either no,^{14,53,54} possible,^{40,55} or strong^{14,56–59} associations with catheter-related thrombosis. Some studies have described weak or possible associations for high factor VIII coagulant activity or anticardiolipin (or antiphospholipid) antibodies,^{40,50} but others have not.^{14,54} Among patients undergoing HSCT, factor V Leiden seems to be a strong risk factor, imparting roughly an 8-fold relative risk for thrombosis with tunneled, long-term CVCs^{56,58} and approximately a 5-fold relative risk with nontunneled, externalized, shorter-term catheters.⁵⁷ No associations were observed with factor V Leiden and clinical thrombosis in patients with various malignancies and either implanted ports,¹⁴ tunneled external catheters,⁵⁴ or various CVCs.⁵³ In contrast, a nested case-control study of women with locally advanced or metastatic breast cancer identified a 6-fold relative risk for catheter-related thrombosis with factor V Leiden.⁵⁹

The prothrombin G20210A mutation was not an independent risk factor in a breast cancer cohort⁵⁹ or in patients with various solid tumors.¹⁴ However, a 2.3-fold relative risk for asymptomatic thrombosis was attributable to the factor II G20210A mutation in a group of 252 patients, including 39 with solid tumors and 97 with hematologic malignancies.⁴⁰ Hyperhomocysteinemia was associated with a 3.8-fold relative risk for catheter-related clinical thrombosis in 1 study.¹⁴ Other trials have not systematically evaluated this abnormality and possible relationships with MTHFR gene polymorphisms.

These observations in adults suggest that patients undergoing HSCT and women with advanced breast cancer have an increased risk for catheter-related thrombosis if they also carry the factor V Leiden mutation. Other patient subgroups with other primary thrombophilic disorders might also be at increased risk.

Treatment-Related Factors

Specific agents seem to increase the risk for CVC-related thrombosis under certain circumstances, including L-asparaginase during induction therapy for ALL;^{48,51,60} estrogen or progesterones in patients with hematologic malignancies;⁶⁰ recombinant human erythropoietin in combination with chemotherapy and radiation in women with cervical cancer;⁶¹ interleukin-2 in patients with melanoma or renal cell carcinoma (particularly those with associated bloodstream infection);⁶² granulocyte-macrophage colony-stimulating factor during peripheral blood stem cell mobilization and collection;⁶³ and thalidomide in combination with corticosteroids or additional agents for myeloma (Table 1).⁶⁴

In addition, heparin-induced thrombocytopenia (HIT) is a significant prothrombotic risk among patients with malignancy,⁶⁵ and upper-extremity DVTs occur in up to 10% of patients with HIT and a CVC.⁶⁶

Diagnosis of Catheter-Related Thrombosis

Clinical Presentation

Symptoms of CVC-related DVT include edema, pain, and erythema of the affected limb, and those associated with upper-extremity devices may include pain and swelling of the neck, supraclavicular area, or head. Chest catheters most commonly induce mural thrombi within the subclavian, axillary, and brachiocephalic veins; less than 15% affect the superior vena cava.³² Proximal arm vein thrombophlebitis is a more common complication with PICCs and peripheral ports.^{6-8,10,11,14} Less frequently, catheter-associated thrombosis presents with clinical signs and symptoms of PE. Symptomatic and asymptomatic PE accompany upper-extremity DVT in roughly 6% and 11% of patients, respectively.⁶⁷

Asymptomatic thrombosis frequently presents with catheter occlusion, but device malfunction does

not always correlate with thrombosis. Fibrin sheath formation and intraluminal fibrin or clot can either totally obstruct flow or cause a “ball-valve” effect.⁶⁷ The latter problem was associated with a 2-fold higher risk for subsequent CVC-related thrombosis among patients with a valved type of catheter.⁶⁸ Similarly, catheter occlusion was noted to precede or accompany thrombosis in 12 of 50 patients with various types of CVCs.³³ Despite these observations, 65% of catheters with nonthrombotic mechanical problems (e.g., caused by malposition) also fail to withdraw blood;⁶⁹ thus, catheter malfunction alone is not a specific indicator of DVT.

Imaging Modalities

Contrast venography is the standard reference test for diagnosing DVT in the upper extremities.⁷⁰ Venographic studies are often constrained, however, by technical and logistical issues, venous access limitations, and concerns of contrast toxicity. Therefore, noninvasive imaging modalities are most frequently used for patients with suspected catheter-associated thrombosis. Compression gray-scale ultrasonography is usually combined with pulsed Doppler signals (i.e., duplex ultrasound) or color Doppler flow imaging (i.e., color duplex ultrasonography) to evaluate for intravascular occlusions and blood flow abnormalities. These techniques can reliably evaluate the jugular, axillary, distal subclavian, and arm veins, but are less sensitive for the proximal subclavian vein, which is obscured by the clavicle. They cannot adequately visualize the brachiocephalic vein or superior vena cava.

A recent systematic review of 5 clinical trials that included 96 patients with CVC-associated thrombosis estimated that duplex ultrasound had an overall sensitivity of 56% to 100% and specificity of 94% to 100%.⁷¹ A prospective study that included 18 patients with malignancy and CVC found that color duplex ultrasonography was 82% sensitive and 82% specific for venographically confirmed DVT.⁷² These data are similar to historical studies of this technique that reported 78% to 100% sensitivity and 88% to 100% specificity.⁷⁰

Despite the reliability of noninvasive testing for most cases, some caveats remain. An isolated flow abnormality on color duplex ultrasonography is nonspecific and mandates contrast venographic assessment.⁷² In addition, no study has yet evaluated the safety of withholding anticoagulant therapy in patients with suspected catheter-associated DVT and a negative duplex ultrasound test. Therefore, contrast

venography, serial follow-up duplex studies, or alternative imaging modality should be performed for these indeterminate cases.^{73,74}

Spiral contrast computed tomography (CT) is useful for evaluating patients with suspected catheter-associated thrombosis involving the brachiocephalic vein or superior vena cava, and those with suspected PE.⁷⁰ However, prospective comparative studies of CT and contrast venography are lacking. Anatomic and technical constraints also limit the ability of contrast CT to accurately visualize more peripheral central vessels and arm veins. Magnetic resonance (MR) techniques, including contrast MR venogram, have also not been proven to be reliable alternatives to more conventional imaging methods for upper-limb DVT.^{70,75} Tortuous venous anatomy, catheter-related flow abnormalities, and motion artifact lead to signal dropout on MR imaging that confounds the detection of thrombosis in this setting.

Prophylaxis of CVC-Related Thrombosis in Patients with Malignancy

Clinical Trial Data and Recommendations

Recent evidence has clarified the role of routine anticoagulant prophylaxis for catheter-associated thrombosis. Table 2 summarizes the relevant retrospective and prospective studies that used specific prophylactic anticoagulant regimens exclusively among patients with malignancies and CVCs, along with defined clinical criteria or imaging modalities to diagnose suspected or occult thromboses.

Among early studies, the prospective, randomized, controlled trial by Bern et al.⁸¹ showed a significant benefit with “mini-dose” warfarin (i.e., 1 mg/d). Similarly, dalteparin, at 2500 IU/d, was effective in the study reported by Monreal et al.⁸² (Table 2). Based on these observations, during the early 1990s through 2001 the consensus panels of the American College of Chest Physicians (ACCP) recommended that prophylactic anticoagulation be used for cancer patients with long-term indwelling CVCs.⁸⁸ However, those recommendations were not widely followed in clinical practice.⁸⁹

Results from more recent retrospective studies and randomized, prospective, placebo-controlled clinical trials (Table 2), in addition to observations from non-randomized or mixed population studies that included adults^{33,40,41} or children⁹⁰ with malignancies, have shown

no benefit with prophylactic warfarin or low-molecular-weight heparins (LMWHs). Therefore, the latest ACCP consensus guidelines in 2004 recommended that routine thromboprophylaxis not be used for this indication.⁹¹

Additional Considerations

The inherent limitations of available trial data, including small study populations, heterogeneous disease groups, and different end points, and the lingering concerns about the relative frequency of asymptomatic clots and their pathophysiologic significance, have prompted recommendations for additional larger studies that focus on specific high-risk patient subgroups and the evaluation of newer antithrombotic agents.^{92–95} In addition, experts have suggested that thromboprophylaxis still be considered for patients believed to be at high risk for catheter-associated complications.^{92–95} Based on risk factors summarized in Table 1, candidate patients might include those with known thrombophilia, prior CVC insertion, prior catheter-associated or noncatheter DVT history, and anatomic or technical risk factors (e.g., bulky perivascular adenopathy, large catheter diameter, line malposition); those undergoing treatment with highly thrombogenic agents (e.g., thalidomide combination regimens); and possibly those with recurrent line-associated infections and occlusive device malfunctions.

Additional considerations derive from studies that observed a lower risk with prophylaxis for certain catheter types. For example, a retrospective investigation found that the rate of clinically overt catheter-related thrombotic complications (including asymptomatic clot detected after imaging for device malfunction) was significantly lower in patients with implanted chest port CVCs who were treated with either prophylactic nadroparin or warfarin (1.3% vs. 33% among those not treated with anticoagulation).¹⁴ Notably, this study showed no benefit from thromboprophylaxis among patients with arm port catheters.

In addition, a prospective, randomized, placebo-controlled trial of short-term, external, nontunneled double-lumen CVCs (duration ≤ 1 month in 63% and ≤ 2 months in 96%) found significantly fewer clinical and asymptomatic thrombotic events among patients treated with a continuous infusion of unfractionated heparin (100 IU/kg/d) compared with those treated with placebo (1.5% vs. 12.6%).⁹⁶

Table 2 Summary of Clinical Trial Data Evaluating the Benefit of Specific Prophylactic Anticoagulation Regimens in Preventing Central Venous Catheter–Associated Thrombosis Among Adult Patients with Malignancies

Study (year)	N Patients	Population	Intervention	Duration	Diagnostic Study	Asymptomatic Thrombosis (%)	Clinical Thrombosis (%)
Retrospective Observational Cohort Studies							
Minassian et al. ⁷⁶ (2000)	305	Gyn malignancies Ext and Port CVCs	Warfarin 1 mg/d	Clinical end point	Duplex or venogram		4/96 (4%) Warfarin* 24/209 (11%) None
Lagro et al. ⁷⁷ (2000)	382	Auto and Allo HSCT	Nadroparin 2850 IU/d × 7 d 5600 IU/d × 10 d	Clinical end point	Duplex		10/123 (8%) Lower dose 7/98 (7%) Higher dose 10/161 (6%) None
Magagnoli et al. ⁷⁸ (2006)	228	Auto HSCT Ext T CVCs	Warfarin 1 mg/d	Clinical end point	Duplex		3/228 (1%) Warfarin (no control group)
Prospective Cohort Studies							
Bozzetti et al. ⁷⁹ (1983)	52	Cancer patients SC CVCs	IV UFH 2500–3100 IU/d vs. none	6–38 days	Venogram	5/15 (30%) Heparin 10/37 (27%) None	0/15 (0%) Heparin 0/37 (0%) None
Nightingale et al. ²¹ (1997)	818	GI malignancies Ext T CVCs	Warfarin 1 mg/d	Clinical end point	Duplex ± venogram		38/818 (5%) Warfarin (no control group)
Boraks et al. ⁸⁰ (1998)	223	Heme disorders Ext T/TNT CVCs	Warfarin 1 mg/d	Clinical end point	Duplex ± venogram		5/108 (5%) Warfarin* 15/115 (13%) Historic controls
Prospective Randomized Controlled Trials							
Bern et al. ⁸¹ (1990)	82	Cancer patients SC Port CVCs	Warfarin 1 mg/d	90 days	Venogram required	4/42 (10%) Warfarin* 15/40 (38%) Control	4/42 (10%) Warfarin* 10/40 (25%) Control
Monreal et al. ⁸² (1996)	29	Cancer patients SC Port CVCs	Dalteparin 2500 IU/d	90 days	Venogram required	1/16 (6%) LMWH* 8/13 (62%) Control	Not specified
Heaton et al. ⁸³ (2002)	88	Heme malignancies Ext T SC CVCs	Warfarin 1 mg/d	90 days	Venogram if indicated		8/45 (18%) Warfarin 5/43 (12%) Control
Mismetti et al. ⁸⁴ (2003)	59	Cancer patients SC Port CVCs	Warfarin 1 mg/d vs. Nadroparin 2850 IU/d	90 days	Venogram required	2/24 (8%) Warfarin 5/21 (24%) Nadroparin (no untreated control)	2/24 (8%) Warfarin 1/21 (5%) Nadroparin (no untreated control)
Verso et al. ⁸⁵ (2005)	385	Cancer patients Ext and Port CVCs	Enoxaparin 40 mg/d vs. placebo	42 days	Venogram required	20/155 (13%) Enoxaparin 22/155 (14%) Placebo	2/155 (1%) Enoxaparin 6/155 (4%) Placebo
Couban et al. ⁸⁶ (2005)	255	Cancer patients Ext and Port CVCs	Warfarin 1 mg/d vs. placebo	Clinical end point during catheter life	Duplex ± venogram if indicated		6/130 (5%) Warfarin 5/125 (4%) Placebo
Karthaas et al. ⁸⁷ (2006)	255	Cancer patients All CVCs	Dalteparin 5000 IU/d vs. placebo	112 days	Duplex or venogram required	10/294 (3%) Dalteparin 6/145 (4%) Placebo	11/294 (4%) Dalteparin 5/145 (3%) Placebo

Abbreviations: Allo, allogeneic; Auto, autologous; CVC, central venous catheter; Duplex, Doppler ultrasound; Ext, external; GI, gastrointestinal; Gyn, gynecologic; HSCT, hematopoietic stem cell transplant; NT, non-tunneled; Port, subcutaneously implanted port; SC, subclavian vein entry; T, tunneled.

*Statistically significant difference between the treatment and control groups.

Safety Issues

Although the clinical indications for prophylactic use of warfarin or LMWH in higher-risk cancer patients with CVCs remain undefined, the use of these agents seems to be relatively safe. Recent randomized, prospective, placebo-controlled trials showed no significant differences among treated patients and controls in the rates of major bleeding complications (range, 0% to 0.7% and 0% to 2%, respectively) or minor bleeding (range, 4% to 17% and 2% to 14%, respectively).⁸⁵⁻⁸⁷ In addition, thrombocytopenia has not been associated with LMWH or unfractionated heparin in this setting.^{84,85,87,96}

Prophylactic warfarin at 1 mg/d can lead to significant elevations in the prothrombin time international normalized ratio (INR). The INR reached 1.5 or more in 20% to 51% of patients with gastrointestinal malignancies taking prophylactic warfarin during treatment with various 5-fluorouracil-based regimens.⁹⁷ Similarly, the INR reached more than 1.5 in 22% of patients with hematologic malignancies undergoing thromboprophylaxis.⁸³ By comparison, only 2% of 130 patients with solid tumors and hematologic malignancies, including 14 who underwent HSCT, experienced an INR more than 2 over a median treatment period of 63 days.⁸⁶ These data suggest that, if monitored appropriately, prophylaxis with LMWH or warfarin can be used safely for selected patients who are considered at high risk for CVC-associated thrombosis.

Management of CVC-Related Thrombosis in Patients with Malignancy

Management of Luminal Occlusion and Fibrin Sheath

Occlusion of the catheter tip by either intraluminal clot or external fibrin sheath deposition can cause complete obstruction of flow or a partial ball-valve effect in the absence of intravascular thrombosis. Device malfunctions of this type are common and, although not specific indicators of thrombosis, can precede or accompany catheter-associated DVT in a high proportion of cases. In the absence of clinical signs or symptoms of DVT or positional, mechanical, and precipitate causes for occlusion, catheter patency can usually be restored with local instillation of a thrombolytic agent.

Prospective, double-blind, placebo-controlled trials that included adult and pediatric cancer patients

showed that catheter patency can be restored with intraluminal doses of alteplase, which is a recombinant tissue plasminogen activator (t-PA), or recombinant urokinase in 85% and 54% of the cases, respectively, without hemorrhagic, embolic, or nonhematologic adverse events.^{98,99} These agents are effective with valved and open-lumen CVCs. Additional retrospective studies of alteplase in young children with cancer¹⁰⁰ and prospective single-arm trials of reteplase, a newer recombinant t-PA variant, in pediatric¹⁰¹ and adult¹⁰² cancer patients showed success rates of 69%,¹⁰⁰ 80%,¹⁰¹ and 95%,¹⁰² respectively. Most cancer centers routinely use standard policies and procedure algorithms to treat asymptomatic CVC occlusions with thrombolytic agents, using the doses and intracatheter dwell times that these studies validated.

Management of DVT and PE

Radiographically confirmed DVT and PE require prompt intervention, regardless of whether the event is associated with catheter occlusion or signs and symptoms of venous obstruction. No prospective, randomized, controlled trial data are available to guide treatment recommendations. Management and treatment algorithms derive from retrospective and prospective observations of upper-extremity DVT in patients with or without cancer and with or without CVCs; anticoagulant approaches for lower-extremity DVT; and expert opinion.^{70,73,74,103} With centrally placed CVCs, the subclavian, axillary, internal jugular, and brachiocephalic veins are most commonly affected; however, clots can be found simultaneously in multiple regional vessels or in different segments of the same vein.¹⁰⁴

The goal of treatment is to prevent or minimize the risks for clot extension, chronic post-thrombotic syndrome, PE, and recurrent DVT while safely maintaining venous access for ongoing antitumor therapy. The rate of post-thrombotic syndrome (i.e., chronic residual pain, swelling, skin discoloration, or ulceration) with catheter-associated DVT is poorly characterized, but ranges from 4% to 10% among cancer patients,^{33,105} and from 6% to 15% among unselected adults^{3,106} and children¹⁰⁷ with catheter-related or upper-extremity DVT. Similarly, the reported incidence of symptomatic PE with CVC-associated DVT varies widely, ranging from as low as 0% in some studies of cancer patients^{33,105} to 17% among unselected children¹⁰⁷ and adults^{67,108} with or without cancer. Notably, the incidence rates of PE with upper-extremity DVT

are the same for clots involving the subclavian, axillary, or internal jugular veins.¹⁰⁹

Initial management of children and adults with CVC-associated DVT or PE should include, unless contraindications exist, therapeutic anticoagulation with unfractionated heparin or LMWH for at least 5 to 7 days followed by transition to LMWH or warfarin.^{70,73,74,103,110} A published outpatient treatment regimen for uncomplicated patients with upper-extremity DVT not specifically catheter-associated used once-daily dalteparin (dosed according to body weight) for 5 or more days, along with warfarin starting on day 1 and subsequent transition to warfarin alone for 3 months (maintaining the INR at 2–3).¹¹¹ Among 46 patients undergoing this treatment in a prospective trial, only 1 developed recurrent DVT (2%) and 1 suffered a major bleeding event (2%).¹¹¹ An alternative approach using initial LMWH followed by 6 months of oral anticoagulation therapy was similarly well tolerated by 36 patients with upper-extremity DVT, with no reported complications of PE, recurrent DVT, or post-thrombotic syndrome.¹¹² Patients with increased risks for bleeding, such as those with chemotherapy-induced thrombocytopenia or a need for an invasive procedure, should be managed judiciously with LMWH¹¹³ or unfractionated heparin. These agents are preferable because of their short half-lives and ability to reverse the effect, at least partially, with protamine.

The importance of initial anticoagulation with a CVC in place and the safety of catheter removal without anticoagulation have not been systematically addressed. One retrospective study of 170 patients with upper-extremity DVT that included 110 patients (65%) with a CVC or pacemaker showed 1-month mortality rates of 10% among those who underwent anticoagulation compared with 24% among those who did not.¹⁰⁶ Notably, although this survival difference supports anticoagulation, the deaths in this study were not caused by fatal PE.

In a retrospective review of treatment outcomes among oncology patients with catheter-associated thrombosis, 20 individuals treated with catheter removal alone experienced no episodes of recurrent DVT during the 2-week follow-up period.¹⁰⁵ By comparison, removal and replacement of a new CVC, without anticoagulation, resulted in persistent thrombotic symptoms in 4 of 12 patients.¹⁰⁵ In this same study, anticoagulation without catheter removal or anticoagulation with catheter replacement resulted

in resolution of clinical signs and symptoms in 100% of 39 and 13 patients, respectively. A recent prospective cohort study showed a similarly favorable outcome among 9 cancer patients who underwent anticoagulation but retained the catheter.³³

The optimal duration of anticoagulation after catheter-associated thrombosis is also undefined. Prospective data from 1 thromboprophylaxis trial⁸⁰ and 1 outcome study³³ indicate that CVC removal and anticoagulation for 3 months⁸⁰ or an unspecified time³³ can effectively prevent symptomatic PE, recurrent DVT, and post-thrombotic syndrome.

Based on these observations, retaining the CVC seems acceptable if the thrombotic complication is not threatening to life or limb, if the line is functional and not infected, and if the patient can safely undergo anticoagulation.^{73,74,110} In this setting, or when the catheter is removed and replaced with another CVC, anticoagulation should be continued for the duration of the catheter or for as long as high-risk prothrombotic factors persist. If the catheter is removed, anticoagulation is recommended for 3 to 6 months.^{70,73,103} The duration may be shorter or longer, however, based on individual assessment of thrombosis severity, bleeding risk, and potential benefit. In patients with contraindications to anticoagulation, the catheter must be removed and the patient monitored for clot progression and PE.¹¹⁴ If the bleeding risk resolves, therapeutic anticoagulation should be carefully started and closely monitored. Patients with progressive thrombosis or PE are candidates for interventional techniques such as mechanical thrombectomy or placement of a permanent or retrievable filter in the superior vena cava.^{70,115,116}

Thrombolytic Therapy

Thrombolytic therapy should be considered for extensive catheter-associated clot that threatens the viability or functional status of the extremity, or for PE associated with moderate-to-severe right ventricular dysfunction.^{70,73,74,103} Although catheter-directed infusion of the fibrinolytic agent may be appropriate for selected patients requiring limb salvage, systemic treatment is otherwise recommended. In all cases, bleeding risks and other potential contraindications must be carefully considered.

The overall benefit, safety, and outcomes of thrombolytic therapy in cancer patients are unknown. In a retrospective cohort analysis of 95 consecutive patients with subclavian–axillary vein thrombosis (including

15% with cancer and 15% with a CVC) who underwent either conventional anticoagulation or systemic urokinase, the thrombolysis group experienced a 60% lower rate of persistent venous occlusion (assessed with ultrasound). However, 21% of those patients also experienced a bleeding complication, whereas none did in the anticoagulation cohort.¹¹⁷ More importantly, the rates of chronic, symptomatic post-thrombotic syndrome were no different between the 2 groups.¹¹⁷ Thus, no long-term advantage for thrombolytic therapy has been shown, and the bleeding risk is considerably higher than with anticoagulation. Notably, recent anecdotal experience suggests that systemic thrombolysis is a very useful adjunct for cancer patients with catheter-related septic thrombophlebitis, in addition to catheter removal and antimicrobials.¹¹⁸

Conclusions

Recent studies indicate that catheter-related symptomatic thromboembolic complications occur at a lower rate than previously observed among general oncology patients. However, specific factors have been identified that increase risk, particularly among certain patient subgroups. Patients who are believed to be at high risk may benefit from thromboprophylaxis, but optimal anticoagulant regimens for either prevention or treatment have not been determined. Properly designed, well-powered prospective trials are needed to address the safety and benefit of LMWH, warfarin, and newer antithrombotic agents among selected patient cohorts with malignancies.

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