ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Management of Thrombosis Associated With Central Venous Catheters in Cancer Patients

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H&O What are the benefits and limitations associated with the use of central venous catheters in cancer patients?

DF Central venous catheters (CVCs) are implanted primarily to allow chemotherapy throughout the duration of cancer treatment. They also can be helpful for supportive care, hydration, pain control, and nutrition. CVCs provide a way to allow parenteral nutrition when required; to deliver adequate antibiotic, antiviral, or antifungal drugs when required in immunosuppressed patients; to administer pain drugs; and to allow blood transfusions to someone who might otherwise not have venous access. The limitations of the use of CVCs are related to the patient's clinical status, venous system, and capacity to support repeated punctures. CVCs cannot be implanted in infected, burned, or previously irradiated areas, in cases of cutaneous metastasis or ipsilateral breast cancer, or in cases of severe blood coagulation abnormalities, septicemia, or previous axillo-subclavian venous thromboembolism.

In cancer patients, the use of long-term CVCs for the administration of intravenous chemotherapy and supportive care treatments has increased. Their use has become a part of daily care for cancer throughout the world. Although I have no official statistics, I would estimate that the number of indwelling catheters has multiplied in the last 10 years.

The benefits and limitations of venous catheters vary according to the type and location of the catheter and the patient's general condition. For example, although a peripherally inserted central catheter (PICC) can be placed at the mid-arm level when no other venous access can be obtained, a recent meta-analysis by Chopra and colleagues of 11 studies comparing the risk of deep vein thrombosis related to PICCs with that related to CVCs showed that PICCs were associated with a higher risk of deep vein thrombosis than are CVCs, especially in patients who are critically ill or those with a malignancy.

The decision to insert PICCs should be guided by weighing the risk of thrombosis against the benefit provided by these devices. The position—above, below, or at the junction of the superior vena cava and the right atrium—and the method of placement will influence the risk of thrombosis. More frequently, a CVC is placed in the subclavian or jugular veins, ideally on the right side of the jugular vein—where the risk of thrombosis appears to be the lowest—or the femoral veins. The risks and benefits also depend on the type of catheter material (eg, open-ended, such as the Hickman catheter, vs a closed-ended catheter with a valve, such as the Groshong catheter), and whether an emerging catheter or a chamber catheter is used.

Rarely, some immediate complications occur following CVC placement. These potential complications include pneumothorax, cardiac arrhythmia, bleeding, air embolism, and malposition. The risk of complications has been shown to relate to the experience of the doctor in charge of positioning the catheter, especially injury to vessels or nerves. Infection, thrombosis, and catheter malfunction, which can also be related to thrombosis, are the most commonly observed late complications.

H&O How often does the use of CVCs lead to thrombosis in cancer patients? Are certain patients at higher risk?

PD The incidence of CVC-related thrombosis in cancer patients varies considerably in the literature. CVC-associated thrombosis, defined as a mural thrombus extending from the catheter into the lumen of a vessel and leading to partial or total catheter occlusion with or without clinical symptoms, varies widely between studies. This is in part related to varying definitions of thrombosis (symptomatic or asymptomatic thrombosis); heterogeneity in study designs (eg, inclusion of fibrin sleeves in some studies); the assorted techniques used to assess central venous catheter-associated thrombosis (eg, venography, ultrasonography); and differences in the definition of CVC-associated thrombosis, study populations, CVC subtypes, and CVC placement methods. In addition, asymptomatic CVC thrombosis may go undiagnosed.

The early studies were performed with various types of diagnostic procedures, including phlebography, which is no longer used. More recent studies using Doppler ultrasound have shown it to be effective in symptomatic catheter-related thrombosis, but to my knowledge it has never been validated for the diagnosis of asymptomatic upper extremity CVC thrombosis. It is important to understand the heterogeneity among these studies. In an early review by Klerk and colleagues, the incidence of symptomatic CVC-associated thrombosis ranged from 0–20% in cancer patients not receiving a prophylactic anticoagulant. Another review by Verso and Agnelli reported an overall incidence of 4–5% (between 0% and 28% depending on the study) for symptomatic events and 30% (between 27% and 66%) for asymptomatic events detected by venography. A prospective study by Evans and colleagues of 2,144 patients with peripherally inserted CVCs found a similar rate of thrombosis, 3%. Most recent trials report similar thrombosis rates, falling in the 3–5% range.

A few studies have demonstrated that the risk of thrombosis is much higher when the CVC is positioned in the femoral vein rather than in the upper vessels. Other factors that affect risk include the experience level of the clinician who is placing the CVC, the use of Doppler ultrasound guidance, and where the catheter is placed in the upper vessels.

H&O Why are international clinical practice guidelines needed for this population?

DF Guidelines are key for assisting practitioners and patients in making decisions about care, and many different national guidelines exist for the treatment of venous thromboembolism in cancer patients. These include guidelines from the Italian Association of Medical Oncology in 2006; the National Comprehensive Cancer Network (NCCN), which have been repeatedly updated; the American Society of Clinical Oncology (ASCO) in 2007 and in 2013; and the American College of Chest Physicians (ACCP) in 2008 and 2012. To my knowledge, the French National Cancer Institute (Institut National du Cancer) guidelines published in 2008 were the first ones to address the specific questions of treatment and prophylaxis of CVC-associated thrombosis in cancer patients, which is critical. Indeed, the onset of CVC thrombosis may notably lead to pulmonary embolism (PE) in 10–15% of patients and loss of the central venous access in 10% of patients. From an economic perspective, it also accounts for a significant increase in direct treatment-related and management costs.

As one of the co-chairs of the Scientific and Standardization Committee's Subcommittee on Hemostasis & Malignancy within the International Society of Thrombosis, in 2009 I proposed that we create international recommendations for the benefit of physicians who live outside of France, Italy, or the United States, such as those living in Asia or South America. I thought this was especially important because none of the recommendations (with the exception of the French guidelines from 2008) had addressed the specific question of CVCs. We pointed this out in a paper published in *Thrombosis Research* in 2010, which included a table that summarized the differences found in guidelines from the NCCN, ASCO, and ACCP, as well as Italian guidelines and the French guidelines from 2008. We thought it was important to pool all the data from the existing guidelines so that the working group could identify areas of consensus and areas of discrepancy. We worked on this for 2 years, using at least 1 expert in oncology and 1 in vascular disease from each European country. We also included our North American colleagues from the United States and Canada, as well as experts from the Middle East. For the rest of the world, experts were asked to review the final report and were associated with the process so as to facilitate further implementation in their own country. The goal was to be able to identify questions that were unanswered in some parts of the world, and to give physicians the best advice based on worldwide knowledge.

H&O Could you please describe the methodology used in gathering the data for the guidelines?

DF First, we set up an international working group that included 24 experts from various specialties, including oncology and hematology. Then we selected our clinical queries and searched the literature with the support of the French National Cancer Institute. Our keywords were *cancer, catheter, venous thromboembolism,* and *anticoagulant drugs*, with the goal of studying treatment and prophylaxis of CVC-associated thrombosis and also of venous throm-

bosis in cancer patients in both the surgical and the medical settings. We reviewed all studies that met our criteria that were published between 1996 and January 2011.

The most important part of the work was the critical appraisal. For each paper in the review, we graded the quality of evidence using an international consensus development method called the Grading of Recommendations Assessment Development and Evaluation (GRADE) system. For each paper, we rated the quality of evidence—whether it was high, moderate, low, or very low—taking into account the study design, study limitations, inconsistency, indirectness, imprecision, and publication bias. For the highest level of evidence (A), further research was very unlikely to change our confidence in the estimate of effect, whereas for the lowest level of evidence (D), any estimate of effect was very uncertain.

All of the participants used a dedicated website that had been specifically designed for us by the French National Cancer Institute so that each member of the working group could check on the criteria by the methodologists. We followed rigorous and standard methodology to identify questions and keywords in common, and the working group members gathered 4 times in 2 years at each step of the process, to validate the grading of each recommendation as strong or weak and to summarize the conclusion. When there was no evidence, we provided "good clinical practice" guidelines. That is how we sorted through the literature on preventing and treating thrombosis in these patients.

H&O What are the various approaches to prevention and management of thrombosis associated with the CVC?

PD This is very important because there are in fact few data for the treatment, and the evidence has changed throughout the years. Based on the evidence that we had obtained in cancer patients with established lower limb thrombosis or PE, we recommended treating symptomatic thrombosis related to the CVC in cancer patients with a minimum of 3 months of anticoagulation. We suggested the use of low-molecular-weight heparin, but stated that oral vitamin K antagonists could also be used.

Another question was whether to keep or remove the CVC. We stated that the CVC can be kept if it is functional, noninfected, and well-positioned, with good resolution of symptoms under close surveillance. Whether the catheter is removed or kept, there is no standard approach in terms of duration of anticoagulation.

As far as prophylaxis is concerned, we had a strong level of evidence that the routine use of anticoagulation to prevent thrombosis in cancer patients with a CVC is not recommended. This was very interesting because we did not think that 20 years ago, or even 10 years ago. The early studies, using phlebography as a diagnostic tool, had suggested that routine anticoagulation was useful, but this was not confirmed thereafter.

We also had a high level of evidence to recommend inserting the catheter in the jugular vein on the right side of the body. As I mentioned earlier, the jugular vein is better than the subclavian vein. Also, the tip of the catheter should be located at the junction of the superior vena cava and the right atrium.

The influence of the position of the catheter tip on CVC-associated thrombosis was assessed in several studies showing a higher rate of thrombosis when the CVC tip was located above the junction between the superior vena cava and the right atrium and that a left-sided insertion as well as femoral vein placement of CVC significantly increased the risk of thrombotic complications. A duration of placement exceeding 25 minutes, more than one CVC placement attempt, previous CVC insertion, CVC blockage use of a triple-lumen (vs double-lumen) CVC and external (vs internal) CVC are significant risk factors for CVC thrombosis. A meta-analysis by Saber and colleagues of 5,636 adult cancer patients fitted with a CVC enrolled in randomized controlled trials showed that, in terms of risk factors for CRT during catheter insertion, implanted ports were better than external catheters, and implantation in the jugular vein was better than implantation in the subclavian vein. Doppler ultrasound guidance of CVC insertion does not seem to confer any advantage except for early complications.

Based on a strong level of evidence, we therefore recommended that for prophylaxis of CVC thrombosis, the catheter should be inserted on the right side in the jugular vein, and the distal extremity of the central catheter should be at the junction of the superior vena cava and the right atrium.

H&O Where can people find out more about the guideline recommendations?

PD We have a website (http://www.thrombose-cancer.com) for people from French-speaking countries that links to the recommendations in both French and English under "International Guidelines." Support was provided by the Groupe Francophone Thrombose et Cancer, the Paris 7 Institut Universitaire d'Hématologie, the International Society of Thrombosis and Haemostasis 2007 Presidential Fund, the Société Médicale des Amis de Desgenettes du Service de Santé des Armées, and the French National Cancer Institute.

H&O Do you anticipate any barriers to implementing these guidelines in clinical practice?

DF I do not see major barriers among patients as long as people have access to health care and anticoagulant drug

delivery, but the key question is how doctors can follow the guidelines in clinical practices. We have to develop specific strategies to implement the guidelines both nationally and internationally. It is up to each country to implement the guidelines according to their local priorities, which in many countries will involve having them adopted by their national health agency.

The world extends beyond North America; we need to think of South America, the Middle East, Africa, India, and China. Their health care systems differ from those of Europe and North America. Having these international guidelines is wonderful because they can be disseminated around the world, especially with the use of new technologies. Right now we are having experts from around the world work to get the guidelines endorsed in their respective countries.

Another factor is access to adequate drugs. The implementation may vary according to whether the practitioners in that country have access to low-molecular-weight heparin or oral vitamin K antagonists, whether they have indwelling catheters and chambers, and whether a national oncology plan is already established or being brought up to date. Different countries will have different priorities.

The key determinant of good implementation for guidelines is the practitioners, particularly their knowledge and their capacity to understand (via several tools, such as accreditation, for instance) the importance of thrombosis in cancer patients at large, as well as the medical and financial consequences of CVC-associated thrombosis in a cancer patient. Having guidelines that are endorsed and reviewed by experts from many different countries should make a big difference in doctors' knowledge. Once we have more information about preventing and treating thrombosis related to CVCs in cancer patients, we will update our guidelines and disseminate them in the same manner.

Suggested Readings

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