Management of venous port systems in oncology: a review of current evidence

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Background: Over the last decades, many changes have occurred in oncology with new chemotherapy combinations and more complex application schemes becoming available. Central venous catheters and implantable venous port systems have become widely used and have facilitated the problem of vascular access. However, important complications are associated with permanent central venous catheters.

Material and methods: This review summarizes evidence on venous port system use published in Medline up to February 2007. Moreover, recent guidelines for the prevention and management of catheter-related infections issued by the Infectious Diseases Society of America, the American College of Critical Care Medicine, the Society for Healthcare Epidemiology of America, the Center for Disease Control and Prevention, Atlanta, and the Infectious Diseases Working Party of the German Society of Hematology and Oncology are included.

Results: Sterile precautions are essential when implanting and accessing port systems. Infections must be treated with adequate antimicrobial therapy. Catheter-related thromboembolic complications were found at a rate of 12–64% in retrospective studies. Five current clinical trials investigated the effect of prophylactic anticoagulation with either low molecular weight heparin or warfarin in cancer patients with central venous devices. On the basis of these results, routine anticoagulation cannot be recommended.

Conclusions: This article reviews the current literature on long-term complications of venous port systems, focusing on infection and thrombosis. In addition, it summarizes the evidence regarding routine maintenance of port systems in follow-up care.

Key words: central venous catheter, chemotherapy, infection, thrombosis, venous port system

Introduction

In 1973, the first long-term central venous catheter (CVC) was used for parenteral nutrition [1]. In 1979, the Hickman catheter, a long-term venous access device, was used for chemotherapy for the first time [2]. The introduction of totally implantable port systems started in the early 1980s [3]. Today, these devices provide easy vascular access for delivery of chemotherapy, fluids, medications, blood products and parenteral nutrition solutions. Over the last few decades, many management changes in oncology have occurred, particularly with respect to new chemotherapy combinations and more complex application schemes. Cancer patients usually require repeated venous punctures for treatment monitoring, application of chemotherapy or blood transfusions. Central venous catheters and implantable port systems have therefore substantially facilitated the problem of vascular access. To date, safe and easy-to-handle port systems have become an integral part of daily clinical routine in oncology [4].

However, there are several rare but nevertheless important complications associated with permanent central venous catheters [5]. After immediate perioperative and short-term complications such as accidental arterial puncture, haematoma, air embolism, pneumothorax or vessel perforation [6], clinical oncologists are most often concerned with major long-term complications occurring during the use of catheters in daily routine care. According to the literature, there is no uniform definition of long-term complications. Therefore, we define long-term complications as complications occurring after the immediate perioperative period following catheter insertion. A retrospective analysis by Yildizeli et al. of 225 catheter and port system implantations detected long-term complications in 6.6% of cases: infection (2.2%), thrombosis (1.3%), extravasation (1.3%) and catheter fracture (1.8%) [7].

Although reviews about venous catheter-related thrombosis exist [8], institutional port implantation and maintenance

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guidelines tend to vary substantially. Therefore, this article reviews the current literature on long-term complications of venous port systems, focusing on infection and thrombosis as well as on their routine maintenance in follow-up care. The important complication of extravasation that still exists with the widespread use of port systems has been extensively discussed in other current reviews [9].

**Method**

Guidelines, recommendations and clinical trials concerning venous port systems and their complications such as thrombosis and infection were searched and reviewed. These data were identified by a Medline search comprising all articles published in English in international journals up to February 2007. The main search terms included ‘central venous catheter’, ‘venous port systems’, ‘thrombotic complications’, ‘thromboses’, ‘infection’, ‘chemotherapy’ and ‘cancer’.

**Discussion**

**Characteristics and use of venous port systems**

Port systems are permanently implantable venous access devices consisting of a port body with silicone membrane and the catheter line itself. Port catheters may be inserted into a number of peripheral veins adhering to maximum sterile precautions and using a cap, mask, sterile gown, sheet and gloves [10, 11]. Implantation is usually possible under local anaesthesia. The port system must be placed in a vessel with a large enough lumen in order to dilute chemotherapeutic drugs and minimize venous damage. Most frequently, the internal jugular or subclavian veins as well as the brachial veins are used [12]. The advantage of implantation in brachial veins is the easy vascular access and a lower risk of immediate complications such as pneumothorax. Kuriakose et al. reported more frequent thrombogenic complications in arm ports than in chest ports (11.4% versus 4.8% respectively) [6, 13]. After implantation, radiological control of the venous port system position is mandatory.

The port system is accessed using a special non-coring Huber needle. The silicone port membrane needs to be punctured vertically in order to avoid bending the tip and care must be taken to observe strictly aseptic precautions (i.e. wearing sterile gloves and disinfecting the skin). It has been shown that 2% chlorhexidine-based preparations reduce catheter-related infections most effectively [14]; however a 70% alcohol solution, an iodophor or a tincture of iodine can be used alternatively [15, 16]. The needle can be kept in place for 72 hours, but should be replaced after 24 hours when used for administering blood products or lipid emulsions [10]. Using a non-coring Huber needle, more than 2000 punctures are possible [10].

**Infections.** According to the literature, the rate of catheter-related infections in long-term central venous access catheters ranges from 0.6 to 27% [7], depending on the catheter type and location and the patient’s constitution. Immunosuppressed patients with port systems were found to have a median of 0.2 infections per 1000 catheter-days (range 0–2.7 per 1000 catheter-days) [17].

Occurring at a rate of 13–14%, bloodstream infections are the third most frequent type of nosocomial infection in the USA and Europe [18, 19]. A large multicentre European study reported that 71% of all sepsis patients had central lines of different types [20]. Catheter-related infections are thus an important problem in the hospital or outpatient setting, contributing to an increased patient morbidity and mortality rate [21]. Therefore, clinicians need to know about prevention, diagnosis and therapy of port system infections. In 2001, the Infectious Diseases Society of America (IDSA), the American College of Critical Care Medicine, the Society for Healthcare Epidemiology of America and the Center for Disease Control and Prevention (CDC), Atlanta, implemented evidence-based guidelines for the prevention and management of intravascular catheter-related infections [10, 22]. The 2003 guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO) cover diagnosis, management and prophylaxis of CVC-related infections in neutropenic patients [23]. The definition of ‘catheter-related infections’ varies considerably among authors and studies; as thoroughly discussed by Faetkenheuer et al., it is necessary to differentiate strictly between catheter colonization (i.e. the presence of bacteria on the catheter surface without bacteremia or clinical signs of inflammation) and true catheter infections, which are subdivided into local infection (i.e. clinical signs of infection at the catheter site without systemic infection), bacteremia/fungaemia (where the same microorganisms are found at the catheter site and in peripheral blood cultures), septic thrombophlebitis and tunnel or pocket infections (defined as spread of the infection into the subcutaneous part of an implanted port system) [23]. In the following we discuss true catheter infections only.

According to a comprehensive review by Bouza et al., catheter infections may be promoted by the following mechanisms: contamination at insertion, which can be avoided by strict antiseptic procedures; migration of skin organisms along the external catheter surface, a pathway less important in port systems than in short-term catheters; contamination of the catheter hub by substances brought into or passing through the catheter lumen, which constitutes the most frequent way of pathogenesis of infection in port systems; contamination by infusate; and finally haematogenous infection from a distant site [17]. Depending on the type of patient and catheter, the main microorganisms responsible for catheter-related infections are coagulase-negative staphylococci, *Staphylococcus aureus* and *Candida* species [17, 23–25].

Diagnosis of a catheter-related infection might be difficult in the absence of local signs of inflammation [17]. In case of fever, all other aetiologies must be ruled out by thorough clinical examination as well as blood and imaging work-up of the patient in order to confirm catheter-related infection as a diagnosis. Paired blood cultures (aerobic and anaerobic) from a peripheral vein and the central catheter should be obtained. If the culture from the central catheter turns positive before the peripheral sample (diagnostic cut-off 2 hours), this so-called differential time to positivity (DTTP) can help to make the diagnosis of catheter-related infection [17,
Clinically stable patient
Unstable patient
Sterile blood cultures
Relapse of infection during/
Absence of local infection
Conditions for catheter removal or salvage in case of catheter-related bloodstream infections

<table>
<thead>
<tr>
<th>Condition</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of local infection signs</td>
<td>Local complications, e.g. tunnel or port infection</td>
</tr>
<tr>
<td>Absence of metastatic complications</td>
<td>Metastatic complications</td>
</tr>
<tr>
<td>Sterile blood cultures</td>
<td>Relapse of infection during/after antibiotic treatment</td>
</tr>
<tr>
<td>Clinically stable patient</td>
<td>Unstable patient</td>
</tr>
<tr>
<td>Mellitus complications</td>
<td>Persistent sepsis/bacteremia</td>
</tr>
<tr>
<td>Certain microorganisms</td>
<td>Certain microorganisms</td>
</tr>
<tr>
<td>S. aureus, Candida species</td>
<td></td>
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</table>

Table 1. Conditions for catheter removal or salvage in case of catheter-related infections

Thromboembolic complications. Another major long-term problem of catheter use in cancer patients is thromboembolic complications. Both infection and thrombosis may lead to significant morbidity and impairment of patients' quality of life. Cancer patients are in general at increased risk of venous thrombosis [33], and placement of a catheter or venous port system further increases this risk. Increased venous stasis, endothelial injury, prothrombotic effects of malignancy and chemotherapy itself are among the factors implicated as causes of thrombosis in cancer patients. Catheter-associated thrombosis manifests itself either as thrombosis of the vein in which the catheter is situated or as an occlusion of the catheter lumen. Venous thrombosis may be asymptomatic or present with ipsilateral arm or neck pain and swelling. Thrombotic occlusion of the catheter lumen may be partial or complete; it may cause restrictions of the catheter's utility and be a starting point for infections or vice versa [34]. The incidence of catheter-associated thrombosis in cancer patients varies considerably between studies and patient or cancer type (Table 2).

Four prospective studies of catheter-associated thrombosis in patients with solid tumours and haematological malignancies report rates of thromboembolic events between 37% and 66% [35–38]. The incidence of catheter-associated thrombosis in retrospective studies varies even more widely (12% to 64%) [39–43].

Table 3, adapted from Agnelli and Verso [8], shows different clinical trials of thrombosis prophylaxis in cancer patients with central venous catheters. In one trial conducted by Monreal et al., cancer patients with central venous catheters were randomized to either low molecular weight heparin once daily for 90 days or no prophylaxis. One of 16 patients in the heparin group (6%) and eight of 13 patients in the control group (62%) developed a thromboembolic event ($P = 0.002$) [38]. Similarly, Bern et al. showed a benefit of the use of 1 mg warfarin for 90 days in cancer patients with central venous catheters. Four out of 42 patients (9.5%) in the warfarin group and 15 of 40 patients (37.5%) in the control group developed thrombosis ($P < 0.001$) [35]. In the majority of patients, there was no increased risk of bleeding associated with warfarin or low molecular weight heparin. According to these two studies, cancer patients with central catheters should routinely receive thromboprophylaxis. Yet the fact that in some patients the prothrombin time was excessively prolonged due to the concurrent use of chemotherapeutic drugs was not separately discussed. Furthermore, neither of the trials was placebo-controlled or double-blind and both analysed only a small number of patients.

Recently, three study groups tried to answer the question of thromboprophylaxis with two prospective, double-blind, placebo-controlled trials. In one trial by Verso et al., 310 patients received either low molecular weight heparin for 6 weeks or placebo. Thrombosis was diagnosed by phlebography in 14.1% in the heparin group compared with...
The rate of symptomatic thrombosis was only 2.1\% [44]. Therefore, the authors speculated that low molecular weight heparin as used in the trial may be ineffective and that a higher dose might have resulted in a positive result. Although this is plausible, the 40 mg daily dose of enoxaparin is considered to be an effective prophylactic dose used after orthopaedic surgery. Moreover, an increased dose could well be associated with an increased risk of bleeding, which was not observed in this trial [45].

Couban et al. chose to use clinical outcome rather than phlebography as the primary endpoint. The choice of two different primary endpoints in the trials by Verso et al. and Couban et al. (phlebography versus clinical outcome respectively) is reminiscent of the endpoint controversy in trials evaluating antithrombotics in orthopaedic surgery [46]. It may be that, in trials evaluating antithrombotic prophylaxis in patients with central vein catheters, symptomatic thrombosis is associated with a better outcome because the natural history of an asymptomatic thrombus on a screening venogram remains unclear. In the trial by Couban et al., patients received 1 mg of warfarin or placebo for 9 weeks. The rate of symptomatic thrombosis in the warfarin patients was 4.6\% compared with 4.0\% in the placebo patients (hazard ratio, 1.20; 95\% CI, 0.37 to 3.94). Once again, the event rate was much lower than expected [47]. Both of these prospective trials show that the rate of catheter-associated thrombosis is relatively low, independent of whether it is measured clinically or radiographically. Moreover, it is necessary to mention complications such as heparin-induced thrombocytopenia (HIT), which is potentially life-threatening in cancer patients [48]. Thus, balancing reasons for and against thromboprophylaxis is essential.

Another prospective, double-blind, placebo-controlled, multicentre study published recently evaluated whether prophylactic treatment with a low molecular weight heparin (dalteparin) could prevent clinically relevant catheter-related thrombosis. In this study 439 cancer patients with a central venous catheter were randomized 2:1 to receive either dalteparin (5000 IU) or placebo once daily for 16 weeks. The dalteparin prophylaxis did not reduce the frequency of thromboembolic complications [49].

A literature search on prophylactic treatment in tumour patients with central venous catheters or receiving chemotherapy did not present evidence to support the use of routine prophylactic anticoagulation for these patients [50]. Chew et al. merged the California Cancer Registry with the American Patient Discharge Data Set and identified breast

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**Table 2.** Incidence of venous catheter-related thrombosis in cancer patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients (n)</th>
<th>Method of diagnosis</th>
<th>Catheter-related thrombosis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bern et al. [35]</td>
<td>42</td>
<td>Phlebography</td>
<td>37.5</td>
</tr>
<tr>
<td>De Cicco et al. [36]</td>
<td>127</td>
<td>Phlebography</td>
<td>66.0</td>
</tr>
<tr>
<td>Balestieri [37]</td>
<td>57</td>
<td>Phlebography</td>
<td>56.0</td>
</tr>
<tr>
<td>Monreal et al. [38]</td>
<td>29</td>
<td>Phlebography</td>
<td>62.0</td>
</tr>
<tr>
<td>Newman et al. [39]</td>
<td>690</td>
<td>Clinical diagnosis</td>
<td>63.5</td>
</tr>
<tr>
<td>Drakos et al. [40]</td>
<td>480</td>
<td>Phlebography</td>
<td>57.2</td>
</tr>
<tr>
<td>Lokich and Becker [41]</td>
<td>53</td>
<td>Clinical diagnosis</td>
<td>41.5</td>
</tr>
<tr>
<td>Kolsky et al. [42]</td>
<td>44</td>
<td>Clinical diagnosis</td>
<td>40.0</td>
</tr>
<tr>
<td>Cortelezzi et al. [43]</td>
<td>416</td>
<td>Clinical diagnosis</td>
<td>12.0</td>
</tr>
</tbody>
</table>

18\% in the placebo group (P = 0.35). The rate of symptomatic thrombosis was only 2.1\% [44]. Therefore, the authors speculated that low molecular weight heparin as used in the trial may be ineffective and that a higher dose might have resulted in a positive result. Although this is plausible, the 40 mg daily dose of enoxaparin is considered to be an effective prophylactic dose used after orthopaedic surgery. Moreover, an increased dose could well be associated with an increased risk of bleeding, which was not observed in this trial [45].

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Table 3. Clinical trials of thrombosis prophylaxis in cancer patients with central venous catheters

<table>
<thead>
<tr>
<th>Reference</th>
<th>Total no. of patients (n)</th>
<th>Method of diagnosis</th>
<th>Therapeutic regimen</th>
<th>Catheter-related thrombosis (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bern et al. [35]</td>
<td>82 (42 vs 40)</td>
<td>Phlebography</td>
<td>Warfarin 1 mg/day vs nil</td>
<td>9.5 vs 37.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Monreal et al. [38]</td>
<td>29 (16 vs 13)</td>
<td>Phlebography</td>
<td>Dalteparin 2500 IU/day vs nil</td>
<td>6.0 vs 62.0</td>
<td>0.002</td>
</tr>
<tr>
<td>Verso et al. [44]</td>
<td>310 (155 vs 155)</td>
<td>Phlebography</td>
<td>Enoxaparin 40 mg/day vs placebo</td>
<td>14.1 vs 18.0</td>
<td>0.35</td>
</tr>
<tr>
<td>Couban et al. [47]</td>
<td>255 (130 vs 125)</td>
<td>Clinical diagnosis</td>
<td>Warfarin 1 mg/day vs placebo</td>
<td>4.6 vs 4.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Karthaus et al. [49]</td>
<td>439 (293 vs 146)</td>
<td>Clinical diagnosis</td>
<td>Dalteparin 5000 IU/day vs placebo</td>
<td>3.7 vs 5.4</td>
<td>0.9</td>
</tr>
</tbody>
</table>

cancer patients diagnosed with thrombosis between 1993 and 1999 to evaluate the incidence of thrombosis and risk factors. Approximately 1% of breast cancer patients developed thrombosis within the first 2 years. Metastases and comorbidities were the strongest predictors for thrombosis [51].

In conclusion, all of these recent studies fail to support the routine use of prophylactic anticoagulation in cancer patients with venous catheters to prevent catheter-induced thrombosis. Institutions should assess their rates of catheter-associated thrombosis and the indication for prophylaxis should be individualized for each patient accordingly. If institutional rates seem to be higher than the rates reported in contemporary trials, institutions may need to re-evaluate how their catheters are inserted and maintained. Central catheters and venous port systems are a mainstay of chemotherapy administration, and thousands of catheters are inserted annually. When symptomatic thrombosis occurs in association with a catheter, it definitely complicates further clinical care of the patient because of the need for anticoagulant therapy and potential catheter-removal. So far, routine prophylactic anticoagulation cannot be recommended based on the available evidence. Large-scale trials like that of Chew et al. using symptomatic thrombosis as an outcome measure are still urgently needed [51].

In addition, there are no data in the literature concerning frequency and management of mere catheter tip thrombosis, where the port system is flushable but no aspiration of blood is possible due to a small thrombus occluding the catheter tip. In our institutions, we administer 5000 IU heparin over 24 hours into the port system via a perfusor system, after which treatment the port system often becomes patent again. However, no further evidence from clinical trials exists to validate this protocol. Moreover, it remains unclear whether catheter tip thrombosis needs to be treated at all since any therapeutic approach is of a merely empirical nature given the lack of any published evidence so far.

**Port maintenance in the follow-up setting.** With permanent venous access devices becoming more widely used, it remains an open question how to manage port systems and maintain their function once they are no longer used for chemotherapy or total parenteral nutrition. In our institutions, we discuss with our patients the option to keep their port systems for as long as 2 years after adjuvant breast cancer therapy owing to the increased risk of relapse within this period, in particular in high-risk patients. Similarly, in metastatic patients with current interruption of their chemotherapy treatment due to good response or stable clinical situation, the port systems will eventually be needed again.

Most manufacturers recommend heparin flushing of the port systems at 4-week intervals [10]. However, according to the literature and our own experience, patients show poor compliance with these inconvenient, time-consuming and expensive monthly appointments. Kuo et al. demonstrated in a retrospective study of 73 patients with gynaecologic malignancies that a 3-monthly protocol for flushing port systems was equally safe and well-accepted. None of their patients was on any anticoagulant therapy. No complications were observed in this study apart from catheter tip thrombosis in seven patients. There was no significant correlation between access intervals and the development of this complication (P > 0.05) [52]. Up to now, the paper by Kuo et al. is the only available publication investigating timing of port flushing in the follow-up setting. Again, to fully answer the question of how often a permanent indwelling device should be accessed during a therapy pause, prospective trials will be necessary.

**Conclusion**

Port systems play an important role in daily care of oncology patients. Several relevant long-term complications exist, namely catheter-related thrombosis, infection, occlusion and skin penetration. Several researchers evaluated the benefit of anticoagulant prophylaxis in patients with permanent venous access devices; however, routine anticoagulation cannot be recommended so far. Infections can be avoided by careful and strict antiseptic handling, thus minimizing contamination. In the follow-up setting, 3-monthly intervals of catheter flushing with heparin seem to be sufficient to keep port systems usable and to prevent thromboembolic complications. Important aspects regarding the care of port catheters and the management of potential complications are summarized in Table 4.

Although clinical management of cancer patients has been facilitated by venous port systems, critical analysis and standardization of port system care on the basis of prospective trials are still necessary to reduce the morbidity and mortality of cancer patients caused by venous port system complications.
Table 4. Important aspects of port catheter care

<table>
<thead>
<tr>
<th>Catheter site care</th>
<th>Thrombosis</th>
<th>Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Strict adherence to sterile precautions</td>
<td>• No recommendation for routine prophylactic anticoagulation</td>
<td>• Catheter removal not always necessary</td>
</tr>
<tr>
<td>• Use of specific non-coring needles</td>
<td>• Treatment with low molecular weight heparin in manifest thrombosis</td>
<td>• Identification of causative microorganisms by blood or catheter tip culture</td>
</tr>
<tr>
<td>• Follow-up care: 3-monthly intervals of port flushing probably sufficient</td>
<td></td>
<td>• Adequate antibiotic therapy</td>
</tr>
</tbody>
</table>

references