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Totally implantable central venous access ports for high-dose chemotherapy administration and autologous stem cell transplantation: analysis of overall and septic complications in 68 cases using a single type of device

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Summary:

Sixty-eight patients suffering from breast cancer, ovarian cancer, lymphoma or multiple myeloma were treated with high-dose chemotherapy and autologous stem cell transplantation. They underwent placement of a central venous port via the subclavian vein for delivery of chemotherapy and reinfusion of stem cells. All patients were followed prospectively for device-related and overall complications, comprising a total of 18 213 days *in situ* (median: 267 days, range: 90–480). One patient experienced a pneumothorax (1.4%) spontaneously resolved, as an acute toxicity. Two patients (2.8%, 0.1 episodes/1000 days of use) were forced to have the port removed due to infection, caused by *Streptococcus mitis* in one case, while the causative agent was not identified by laboratory tests in the second. The other 66 patients completed the therapeutic programme, including peripheral stem cell reinfusions and supportive care, such as i.v. antibiotics, antiemetics or fluid administration and blood sample collection, without additional complications. In conclusion, the use of totally implantable central venous access ports has resulted in good long-term access to central veins, in spite of the severe neutropenia and increased septic risk of this category of oncology patients.

Keywords: central venous catheters; ports; high-dose chemotherapy; autologous stem cell transplantation

Central venous access is always necessary for the management of patients undergoing high-dose chemotherapy (HDCT) with concomitant BMT (bone marrow transplantation) or autologous PBSCT (peripheral blood stem cells transplantation). The systematic use of these devices reduces the need to enter the venous system to draw blood samples and administer cytotoxic drugs, antibiotics, blood products, fluids, and nutrition, which are essential parts of therapy. Moreover, high-flow venous catheters may also be used for the collection of peripheral stem cells. Tunneled, cuffed silastic catheters, first described by Broviac *et al*[1] and subsequently modified by Hickman *et al*[2] provide trouble-free function for most patients undergoing BMT and currently represent the most frequently adopted intravenous line for these patients.[3–5] The increased demand among clinical oncologists for totally implantable access ports (TIAP) in respect to percutaneous tunneled catheters is motivated from the evidence that they need no external dressing, allow patients normal activities improving their quality of life and are easy to maintain on a 3-monthly basis. Ports are now extensively used for delivering standard or infusional chemotherapeutic regimens in solid tumors patients,[6] whereas there are very few studies and little data concerning the use of TIAP in patients undergoing high-dose chemotherapy and PBSCT or BMT.[7,8] A possible explanation could be the fact that TIAP cannot be easily withdrawn, unlike cuffed or non-tunneled catheters, when an infectious catheter-related complication occurs. In addition, the crude cost of TIAP is much higher than tunneled, cuffed external devices, although comparative and comprehensive economic evaluations are not available to date.[9,10] Moreover, most studies do not involve a sufficiently long follow-up, whereas it is well known that a number of late port or tunneled catheter-related complications arise some weeks or even months after implantation. Last, but not least, nobody has previously investigated the possibility of using these devices not only to administer chemotherapy but also for PBSC reinfusion and supportive care. The aim of this study was to examine prospectively the use of TIAPs, by presenting the experience of a single institution with a single type of device in a number of consecutive patients who underwent HDCT and BMT.

Patients and methods

Sixty-eight cancer patients treated with HDCT and autologous stem cell transplantation at the European Institute of Oncology in Milan during a 12-month period from 1 January to 31 December 1997 received a TIAP implant and were followed prospectively for device-related and overall complications. Patient characteristics and HDCT regimens used are shown in Table 1.

All devices were placed in the operating room under

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Table 1 Population characteristics, types of tumors and chemotherapy programmes

No. of ports	68
No. of patients	68
Age (years, mean)	41.8
range	22–62
Male:female ratio	8:60
[a]Sequential chemotherapy for lymphoma[33]	10
[b]L-PAM chemotherapy for myeloma[34]	1
[c]High-dose EC chemotherapy for breast cancer	15
[d]High-dose ICE chemotherapy for breast or ovarian cancer	35
Different high-dose chemotherapy for breast cancer	7

[a]CTX 7 g/m^2 + MTX 8 g/m^2 + VP-16 2 g/m^2 + (Ida i.c. 15 mg/m^2/day + L-PAM 180 mg/m^2 + PBSC support).
[b]Alkeran 200 mg/m^2 + PBSC support in a single or double transplant.
[c]Iphosphamide 2500 mg/m^2 + carboplatin 300 mg/m^2 + etoposide 300 mg/m^2 + PBSC support repeated every 28 days for three cycles.
[d]Epirubicin 200 mg/m^2 + cyclophosphamide 4 g/m^2 + PBSC support repeated every 28 days for three cycles.

fluoroscopic control by the same operator (RB); a single dose of Cefazoline sodium (2 g) was given i.v. 15 min before implantation. No breaks in operative technique or instrument sterility were documented.

A single type of port was used, constructed from titanium and silicone rubber, connected to a 7.8 F polyurethane catheter (Port-A-Cath, SIMS Deltec, St Paul, MN, USA).

A confirmatory chest X-ray was always obtained after the placement and a central venous access form was filled in by the operator after the procedure. Data from the follow-up of the patients were recorded on the form and collected in a software registry. Follow-up was continued until the device was removed, the patient died or the study was closed (30 June 1998).

Complications were classified into two main categories: (1) early (intraoperative and post-implantation period to first use), and (2) late complications (occurring after the first chemotherapy course given through the device).

Blood samples for microbiological analyses were obtained when clinically indicated, in particular when patients experienced fever with or without signs of systemic sepsis. Criteria for the diagnosis of device-related bacteremia were defined as: (1) greater than a 10-fold increase in colony-forming units (CFU) of bacteria per ml of blood obtained through the device in comparison to peripheral blood cultures; or (2) greater than 1000 CFUs of bacteria obtained through the device, in the absence of peripheral blood cultures; or (3) positive catheter tip culture upon removal in the appropriate clinical setting. Device-related bacteremia was considered cured when culture results were negative on discontinuation of antimicrobic therapy and no evidence of clinical infection occurred in the following 2 weeks.

Port pocket infection was defined as induration, erythema, and tenderness around the port with culture-positive material aspirated from the port pocket.

Cutaneous site infection was defined as induration, erythema, or tenderness and exudate at the port surface needle access site.

Thrombosis was detected with ultrasound and/or venography when clinically suggested by progressive arm or facial swelling.

Table 2 Duration of use of ports and route of central vein catheterization

No. of ports	*68*
Days *in situ* (mean)	267
range	90–480
Days *in situ* (overall)	18,213
Percutaneous catheterization[a]	62
Surgical venous cut-down (cephalic vein)	6 (10%)

[a]Percutaneous subclavian vein catheterisation first described by Aubaniac.[28]

Results

Sixty-eight devices were placed in 68 patients, resulting in a total of 18 213 days *in situ*, and adequate follow-up was obtained in all the cases (mean: 267 days, range: 90–480).

Table 2 summarizes pertinent device characteristics and routes for central venous access. All patients received the planned chemotherapy and re-infusion of stem cells through the TIAP. We did not observe any TIAP-related deaths in this series. An asymptomatic pneumothorax (less than 30% of the pleural space) was observed as a complication of the TIAP placement in one patient, but this single patient did not need any additional procedure except for clinical observation and chest X-ray monitoring.

One patient in this series had an accidental arterial puncture during the implantation procedure, which did not cause any significant complications. If any doubt existed about arterial *vs* venous cannulation, our policy was to withdraw the wire and needle rather than risk the creation of a large hole in the artery with a dilator.

No cases required early revision of the implant, for malfunction of the catheter due to a narrowing of the lumen or dislocation.

Late complications observed in our experience are listed in Table 3. Interestingly, catheter rupture and embolization did not occur at all and neither did clinically evident catheter-associated venous thrombosis.

Port pocket infection, usually caused by gram-positive cocci, suggests direct inoculation or migration of organisms

Table 3 Late complications observed in this series

Complication	*No.*	*% of devices*	*/1000 days of port use*	*Actions taken*
Catheter rupture – migration	0			
Symptomatic venous thrombosis	0			
Pocket infection	1	1.4	0.05	port removal
Skin erosion	0			
Port-related bacteremia[a]	1	1.4	0.05	antibiotics and port removal after completing the treatment
Total	2	2.8	0.10	
Devices still *in situ* (30 June 1998)	49	72		

[a]Infection was caused by *Streptococcus mitis*.

along the accessing needle as the primary mechanism. It occurred once in this series, 90 days after implant (1.4%, 0.05 episodes/1000 days of use); the causative agent was not identified by laboratory tests, although a purulent discharge was collected from the port subcutaneous pocket. The device was removed and the infection successfully cured, with no additional morbidity.

Nine patients developed febrile neutropenia of unknown origin (FUO), while only one suffered from port-related bacteremia (1.4%; 0.05 episodes/1000 days of port use), due to *Streptococcus mitis.* The infection occurred 25 days after the implant, and was successfully treated with appropriate systemic antibiotics; the port was removed after completing the therapeutic programme.

Interestingly, all the patients received therapeutic support through the port such as antiemetics, fluids, platelets and red blood cells transfusions, antibiotics; blood samples were regularly collected. No problems were reported during or following these procedures. This resulted in a significant improvement in the quality of life of the patients, allowing them to move their arms and to attend to daily care more easily. In four cases only out of 68 it was necessary to give 25 000 IU of urokinase to remove fibrin from the catheter and restore normal flow through the device.

After discharge of the patient, the TIAP was washed with normal saline just once every 3 months, and complete function was maintained.

Discussion

Device-related morbidity reported in the literature is difficult to compare because of varying definitions and dissimilar patient populations. Compared to tunneled catheters, port infections tend to be unusual,[11] even if results are sometimes conflicting[12] and most series reflect differences in the type of device used and patients being treated, rather than any inherent superiority of one device over another. Moreover, it is likely that the patients requiring more intensive treatment such as those with hematologic malignancies, severe neutropenia or bone marrow transplants, are candidates to receive tunneled double-lumen Hickman catheters, which are much more easy to remove than are ports, and allow high flow. The negative role of neutropenia was emphasized by a study of nosocomial septicemia in cancer patients, which reported that 61% of septic episodes in patients with central venous lines occurred when the patients were neutropenic.[13] Moreover, high-dose chemotherapy, multiple blood tests and transfusions are more feasible with a larger bore catheter. For these reasons, Hickman's catheter or similar devices currently represent the most frequently used intravenous lines for patients undergoing bone marrow transplantation. While several retrospective studies have noted higher infection rates for external devices compared to TIAP in selected patient populations,[11,14], a prospective randomized study was unable to demonstrate a statistically significant difference in incidence of infections.[15] They appeared much more common for both Hickman catheters and ports than many other reports, probably due in part to a study population that included many patients with hematologic malignancies. In a randomized study of infectious morbidity in patients with solid tumors, TIAP have been shown to be associated with fewer infections than were catheters.[16] Most often, these septic events are due to bacteremias that develop from sites of microbial invasion remote from the catheter itself and which usually respond to appropriate antibiotics without the need for catheter withdrawal;[17,18] removal may be necessary for persistent or recurrent bacteremia or for fungal infections. In spite of accurate implant procedure and appropriate post-implantation care, catheter-related infections are reported in 11–45% of patients with Hickman catheters,[11,15,19,20] 0–22% of patients with TIAP[11,15,21,22] and 7–32% of patients with Groshong catheters.[19,21,23,24,25] BMT recipients are particularly prone to developing catheter-related infectious complications; usually they exceed 20% for subcutaneously tunneled devices.[8,26] Non-tunneled catheters have been recently proposed for patients undergoing BMT,[27] because they can be easily inserted and withdrawn without surgery; conversely, they were associated with a 15% catheter-related infection rate. Data from this study, derived from a prospective non-randomized study, support the conclusions of most retrospective papers: the infectious morbidity related to TIAP is very low, even in patients undergoing cytostatic treatments for solid tumors. The mechanisms of device-related infection may explain why TIAP are less likely to be associated with infection than are tunneled catheters. Migration of skin flora through the cutaneous insertion site with catheter colonization is supported by the finding that gram-positive organisms, especially coagulase-negative staphylococci are responsible for a significant percentage of the cases of device-related bacteremia in patients with catheters. Compared with catheters, TIAP are irrigated less frequently, require no home care, and are less prone to environmental or cutaneous contamination when not accessed. All these factors may contribute to the reduced incidence of infections associated with TIAP.

Fluoroscopy has been always used at time of insertion of the central venous catheter to immediately check the correct position of the tip, even if post-implant confirmatory chest X-ray is always obtained. Although the success rate of 'blind' insertion of the catheter may be quite high and this approach could avoid the additional cost of ultrasound or fluoroscopy, the routine use of fluoroscopy allowed us to avoid time-consuming, patient-stressing and very expensive repositioning of the device after post-implant radiologic demonstration of its wrong location in the contralateral brachiocephalic vein or in the ipsilateral internal jugular vein. Moreover, since 1989 there has been a formal warning from FDA-USA to avoid the intra-atrial location of the catheter tip and this may be easily accomplished with the rigorous use of fluoroscopic intraoperative control.

The incidence of symptomatic catheter-related venous thrombosis was zero in this study (Table 3); no useful data are available from retrospective analyses of clinical and autopsy reports, where the incidence varied from 0 to 50%.[29,30] In a controlled randomized trial, prospective venography was performed as part of a study of prophylactic low-dose warfarin, with a symptomatic thrombosis rate in untreated patients of 12.5% and an overall rate (symptomatic + silent) of 38% (15 of 40).[31] Another pro-

spective study in cancer patients, using the same device (Port-a-Cath subclavian venous catheter) reported 62% upper extremity deep vein thrombosis in the control group, and 6% in patients taking 2500 IU subcutaneous Fragmin once daily for 90 days (relative risk 6.75; $P = 0.002$, Fisher exact test.[32]) Clinical data derived from our study are not fully comparable, due to different patient populations and absence of regular US scan or phlebografic monitoring, thus limiting the diagnosis of venous thrombosis to clinically obvious cases; however, they do not support the routine use of low dose anticoagulants in patients bearing a TIAP, at least in this clinical setting (high-dose chemotherapy and PBSCT).

From the patients' point of view, use of these devices results in a great improvement in quality of life, both during hospitalization and at home, between chemotherapy cycles. Since this patient population is often at high risk of relapse, we suggest that the device is maintained *in situ* for at least 2 years, even though such a decision is always taken with the patient, based on his/her compliance.

New to this report is the possibility of reinfusing PBSC and transfusing platelets and blood via the TIAP, without any significant complications. In conclusion, the use of totally implantable ports has resulted in good long-term access to central veins and delivery of high-dose chemotherapeutic regimens with concomitant autotransplantation of stem cell, in spite of the severe neutropenia and increased septic risk of this category of oncology patients. Although multicentric randomized clinical trials are needed to define optimal devices in this clinical setting, the results of this prospective, non-randomized study support a wider use of TIAP in oncology patients undergoing high-dose chemotherapy and autologous stem cell transplantation.

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