Use of totally implantable central venous access ports for high-dose chemotherapy and peripheral blood stem cell transplantation: results of a monocentre series of 376 patients

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Background: The complication rate of central venous totally implantable access ports (TIAP), used for high-dose chemotherapy with autologous stem cell transplantation support, has not been fully investigated to date, due to the almost exclusive use of externalised, tunnelled devices in this clinical setting.

Patients and methods: During a 66-month period (from 1 January 1997 to 30 June 2002), 376 patients suffering from breast cancer, ovarian cancer, lymphoma or multiple myeloma were treated with high-dose chemotherapy and autologous stem cell transplantation at the European Institute of Oncology (Milan, Italy). 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, Inc., St Paul, MN, USA) inserted into the subclavian vein. They were followed prospectively for device-related complications until the device was removed, the patient died or the study was closed (30 June 2002).

Results: No TIAP-related deaths were observed in this series. Seven pneumothoraxes (1.8%) occurred as a complication of TIAP placement, one patient only (0.2%) requiring a tube thoracostomy. Port pocket infection occurred twice in this series (0.53%, 0.01 episodes/1000 days of use), whereas three patients suffered from port-related bacteraemia (0.8%, 0.016/1000 days of use). Infections were successfully treated with antibiotics; all three cases had the ports removed at programme completion. Four cases of deep vein thrombosis were detected (1.06%, 0.022/1000 days of use); low molecular weight heparin was given, followed by oral anticoagulants. Finally, one case of extravasation occurred (0.26%, 0.005/1000 days of use), requiring port removal and local medical therapy.

Conclusions: The use of TIAPs has resulted in a safe and effective option for high-dose chemotherapy delivery and stem cell transplantation, in spite of inducing severe neutropenia and increasing the risk of sepsis in this category of oncology patient.

Key words: central venous catheters, high-dose chemotherapy, peripheral blood stem cells transplantation, ports

Introduction

A central venous access is always necessary for the management of patients undergoing high-dose chemotherapy (HDCT), with concomitant bone marrow transplantation (BMT) or autologous peripheral blood stem cells transplantation (PBSCT), as it allows for easy drawing of blood samples and administration of drugs, antibiotics, blood products, fluids and nutrition; all essential parts of the therapeutic programme. Tunnelled, cuffed silastic catheters (Hickman-Broviac, Bard Inc., Salt Lake City, UT, and similar devices) provide trouble-free function for most patients and currently represent the most frequently adopted intravenous line [1, 2]. There are very few studies and little data concerning the use of totally implantable central venous access ports (TIAP) in patients undergoing HDCT and autologous PBSCT or BMT [3]; a possible explanation for this is that TIAP cannot be easily withdrawn, unlike cuffed or non-tunnelled catheters, when an infectious catheter-related complication occurs. In addition, their crude cost is much higher than tunnelled, cuffed external devices, although comparative and comprehensive economic evaluations are scanty. The aim of this study was to investigate, in a prospective way, the use of TIAP in this clinical setting, analysing the relevant number of consecutive patients treated at a single institution with a single type of device.

Patients and methods

At the European Institute of Oncology (Milan, Italy), 376 cancer patients were treated with HDCT and autologous PBSCT during a 66-month period from 1 January 1997 to 30 June 2002. Patient characteristics and the HDCT regimens
used are reported in Table 1. Each patient underwent the placement of a single type of TIAP, constructed from titanium and silicone rubber, connected to a 7.8 F polyurethane catheter (Port-A-Cath™; SIMS Deltec, Inc., St Paul, MN, USA), inserted in the subclavian vein. All devices were placed under local anaesthesia in the operating room and employing fluoroscopic control by three experienced surgeons (R.B., S.P. and U.P.) using maximal sterile-barrier precautions. A confirmatory chest X-ray was always obtained after placement and a central venous access form was filled in by the operator after the procedure. A single dose of cefazolin sodium 2 g was given intravenously 15 min before implantation. No breaks in operative technique or instrument sterility were documented. Our institutional policy restricts the use and maintenance of ports to specialised nursing staff, who always perform the blood withdrawals for laboratory testing. To prevent clot formation and catheter blockage, TIAPs were flushed with 20 ml normal saline and then filled with sterile heparinised saline after each infusion of medication or blood withdrawal (5 ml of a solution containing 50 IU/ml heparin). Data from the follow-up of patients were recorded at regular intervals and collected in a software registry, with specific attention to device-related and overall complications. Follow-up was continued until the device was removed, the patient died or the study was closed (30 June 2002).

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

Blood screening for bacteraemia was not performed at regular intervals since blood sampling for microbiology was obtained when clinically suggested (unexplained fever and/or signs of sepsis). Intravenous antimicrobial therapy, including amikacine and ceftazidime, was initiated empirically in febrile neutropenic patients suffering from lymphoma or myeloma, whereas piperacillin-

tazobactam was used for patients affected by solid tumours. An appropriate systemic antibiotic therapy was subsequently started, based on the susceptibility of the isolate, if any. Criteria for the diagnosis of device-related bacteraemia were defined as follows: a, a >10-fold increase in colony-forming units (c.f.u.) of bacteria per ml of blood obtained through the device in comparison to peripheral blood cultures; b, >1000 c.f.u. of bacteria obtained through the device, in the absence of peripheral blood cultures; or c, positive catheter tip culture upon removal in the appropriate clinical setting. Device-related bacteraemia was considered cured when culture results were negative at the discontinuation of antimicrobial 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. Prophylaxis for venous thromboembolism (i.e. daily minidose oral warfarin or subcutaneous low molecular weight heparin) was not applied in this study population.

Results

Three hundred and seventy-seven devices were placed in 376 patients (304 female, 72 male), resulting in a total of 178.065 days in situ; adequate follow-up was obtained in all cases (mean, 473 days; range, 1–1419) and all patients except one received the planned chemotherapy and re-infusion of stem cells through the TIAP. Devices still in situ at the end of follow-up were 232 (61.5%); death occurred in 82 patients (21.7%), while 11 ports (2.9%) where prematurely removed as a consequence of complications and 52 devices (13.7%) were removed after the conclusion of the planned treatment (Table 2).

Early complications

We did not observe any TIAP-related deaths in this series. A pneumothorax was observed as a complication of TIAP placement in seven patients (7/377, 1.8%); one patient only (0.2%) required a tube thoracostomy to treat a large pneumothorax, with no additional morbidity. One patient experienced an atrial fibrillation as a consequence of the port implant; it was successfully treated with port removal and re-implantation on the opposite side. Finally, one patient had an accidental arterial puncture during the implant procedure, which did not cause any significant complication.

### Table 1. Population characteristics, type of tumour and chemotherapy programmes

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of patients</th>
<th>Age, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>376</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>41.8</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>22–62</td>
<td></td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>72/304</td>
<td></td>
</tr>
<tr>
<td>Sequential chemotherapy for lymphoma ≥5</td>
<td>79 (21)</td>
<td></td>
</tr>
<tr>
<td>Ly-PAM chemotherapy for myeloma ≥5</td>
<td>14 (3.7)</td>
<td></td>
</tr>
<tr>
<td>High-dose EC chemotherapy for breast cancer (± Taxotere)</td>
<td>153 (40.7)</td>
<td></td>
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<tr>
<td>High-dose ICE chemotherapy for breast or ovarian cancer (± Taxotere)</td>
<td>85 (22.6)</td>
<td></td>
</tr>
<tr>
<td>Different HDC for breast cancer, n (%)</td>
<td>24 (6.5)</td>
<td></td>
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<tr>
<td>Different HDC for other tumours, n (%)</td>
<td>21 (5.5)</td>
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*CTX 7 g/m², MTX 8 g/m² and VP-16 2 g/m² (Idarubicin i.c. 15 mg/m²/day + Ly-PAM 180 mg/m² + PBSC support).

1Alkeran 200 mg/m² plus PBSC support in a single or double transplant.

1Ifosfamide 2500 mg/m², carboplatin 300 mg/m², etoposide 300 mg/m² and PBSC support repeated every 28 days for three cycles.

1Epirubicin 200 mg/m², cyclophosphamide 4 g/m² and PBSC support repeated every 28 days for three cycles.

CTX, cyclophosphamide; HDC, high-dose chemotherapy; MTX, methotrexate; Ly-PAM, melphalan; PBSC, peripheral blood stem cells; VP-16, etoposide.

### Table 2. Details of port use

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of ports, n (%)</th>
<th>Days in situ (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of ports</td>
<td>377 (100)</td>
<td></td>
</tr>
<tr>
<td>Days in situ</td>
<td>473</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>1–1419</td>
<td></td>
</tr>
<tr>
<td>Devices still in situ (30 June 2002), n (%)</td>
<td>232 (61.5)</td>
<td></td>
</tr>
<tr>
<td>Devices removed for complications, n (%)</td>
<td>11 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Devices removed after completion of treatment, n (%)</td>
<td>52 (13.7)</td>
<td></td>
</tr>
<tr>
<td>Deceased patients, n (%)</td>
<td>82 (21.7)</td>
<td></td>
</tr>
</tbody>
</table>
Furthermore, no cases required an early revision of the implant for malfunction of the catheter due to a narrowing of the lumen or primary dislocation.

**Late complications**

Late complications observed in this study are listed in Table 3. Port pocket infection occurred twice in this series (0.53%, 0.016/1000 days of use); the causative agent was not identified in one case by laboratory tests, although a purulent discharge was collected from the port’s subcutaneous pocket. The other case was caused by *Staphylococcus epidermidis*. The devices were removed and the infection successfully cured, with no additional morbidity.

Twenty-eight patients developed febrile neutropenia of unknown origin (FUO), while only three suffered from port-related bacteraemia (0.8%, 0.016/1000 days of port use). Causative agents were *Streptococcus mitis* and *S.epidermidis* (two cases). The infections occurred 25–38 days after implantation, and were successfully treated with the appropriate systemic antibiotics; the ports were removed after completing the therapeutic programme.

Four cases of deep vein thrombosis have been detected (1.06%, 0.022/1000 days of port use), at varying intervals after port placement (range 14–35 days). Low molecular weight heparin was given, then to obtain a therapeutic INR (International Normalized Ratio), oral anticoagulants were administered for 3 months. Ports were always removed. Finally, one case of extravasation occurred (0.26%, 0.005/1000 days of port use), requiring port removal and local medical therapy. All patients received therapeutic support through the port, such as antiemetics, fluids, platelets and red blood cells transfusions, and antibiotics; blood samples were regularly collected. No problems were reported during or following these procedures. In only 12 of 376 cases has it been necessary to apply 25,000 IU urokinase to remove fibrin from the catheter and restore normal flow through the device.

After discharge of the patient, washing the TIAP just once every 3 months with normal saline maintained its complete functionality.

**Discussion**

Tunneled, cuffed silastic catheters (Hickman-Broviac and similar devices) currently represent the most frequently adopted intravenous line for patients undergoing HDCT with concomitant BMT or autologous PBSCT [1, 2], as multiple blood tests, transfusions and nutrition are more easily accomplished with a larger bore catheter, allowing high flow and easy removal, with a cuff and a subcutaneous tunnel limiting the possibility of catheter-related infections. The innovative use of TIAP in this clinical setting, based on a small series of patients, has been previously reported by our group [3]; the present paper is an update of that initial experience and represents the largest published series of TIAP used for HDCT deliverance with concomitant PBSCT. With a lack of well designed and appropriately powered randomised trials, it is difficult to compare different device-related morbidity; data reported in the literature are sometimes conflicting [4–7]—most series reflecting differences in the patient populations being treated, rather than superiority of one device over another. Compared to tunneled catheters, port infections tend to be lower; several retrospective studies have noted higher infection rates for external devices compared with TIAP in selected patient populations [8, 9], but a prospective randomised study was unable to demonstrate a statistically significant difference [10]. This study showed that infection rates are much higher for both tunneled catheters and ports than reported by others, in part due to the fact that the vast majority of the patient population had haematological malignancies. The active, negative role of neutropenia in promoting catheter-related infections was clearly demonstrated by a study of nosocomial septic events in cancer patients: 61% of septic episodes occurred when the patients were neutropenic [11].

In a randomised study of infectious morbidity in patients with solid tumours, TIAP have been shown to be associated with fewer infections than were catheters [12]. Most often, these septic events respond to the appropriate antibiotics without the need for catheter withdrawal [13, 14]; removal may be necessary for persistent or recurrent bacteraemia or for fungal infections. In spite of an accurate implant procedure and appropriate post-implantation care, catheter-related infections are reported in 11–45% of patients with Hickman catheters [10, 14, 15], 0–22% of patients with TIAP [7, 10, 16–18] and 7–32% of patients with Groshong catheters [Bard Inc., Salt Lake City, UT; 14, 16, 19–22]. BMT recipients are particularly prone to developing catheter-related infectious complications; usually they exceed 20% for subcutaneous tunneled devices [8, 23]. Non-tunneled catheters have been recently proposed for patients undergoing BMT [24] as they can be easily inserted and withdrawn without surgery; conversely, they exhibited a 15% catheter-related infection rate. Data from our study, derived from a large, prospective, non-randomised study, support the conclusions of most retrospective papers: the infec-

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**Table 3. Late complications**

<table>
<thead>
<tr>
<th>Complication</th>
<th>No.</th>
<th>%</th>
<th>/1000 days of port use</th>
<th>Actions taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep vein thrombosis</td>
<td>4</td>
<td>1.06</td>
<td>0.022</td>
<td>Anticoagulation and port removal</td>
</tr>
<tr>
<td>Pocket infection</td>
<td>2</td>
<td>0.53</td>
<td>0.010</td>
<td>Antibiotics and port removal</td>
</tr>
<tr>
<td>Port related bacteraemia</td>
<td>3</td>
<td>0.8</td>
<td>0.016</td>
<td>Antibiotics and port removal</td>
</tr>
<tr>
<td>Extravasation</td>
<td>1</td>
<td>0.26</td>
<td>0.005</td>
<td>Removal and local treatment</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>2.65</td>
<td>0.053</td>
<td></td>
</tr>
</tbody>
</table>
tious morbidity related to TIAP is very low, even in patients undergoing HDCT. Compared with externalised 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. It should be underlined that ~75% of the patients we have treated suffered from solid tumours (Table 1), with relatively short durations of neutropenia. As the majority of studies using Hickman catheters (i.e. tunneled central venous externalised catheters) refer to haematology/oncology patients with longer neutropenia, this may in part explain the good results obtained here.

The incidence of catheter-related symptomatic venous thrombosis has been quite low in this study (Table 3); no useful data are available from retrospective analyses of clinical and autopsy reports in the medical literature, where the incidence varied from 0 to 50% [25, 26]. In a controlled randomised trial, prospective venography was performed as part of a study of prophylactic low-dose warfarin treatment, with a symptomatic thrombosis rate in untreated patients of 12.5% and an overall rate (symptomatic plus silent) of 38% (15 of 40) [27]. Another prospective study in cancer patients using the same device (Port-a-Cath™ subclavian venous catheter) reported a rate of upper extremity deep vein thrombosis of 62% 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’s exact test [28]). Clinical data derived from our study are not fully comparable, due to differences in the patient populations and absence of regular ultrasound scans or phlebographic monitoring, thus limiting the diagnosis of venous thrombosis to clinically relevant cases; however, they do not support the routine use of low dose anticoagulants in patients bearing a TIAP [29], at least in this clinical setting (high-dose chemotherapy and PBSC).

The possibility of reinfusing PBSC and transfusing platelets and blood from the TIAP without any significant complications has been confirmed by this study, thus demonstrating a new use for this kind of device. However, it should be noted that single-lumen TIAPs can not be used for apheresis; it was performed in our series through peripheral veins whenever feasible, and a double-line, 14 F polyurethane catheter was inserted in the internal jugular vein as a bedside procedure when peripheral veins were not suitable for apheresis.

In conclusion, the use of totally implantable ports has resulted in a good option for long-term access to central veins and delivery of high-dose chemotherapeutic regimens with concomitant autotransplantation of stem cells, in spite of severe neutropenia and increased risk of sepsis in this category of oncology patients. Although multicentre randomised clinical trials are needed to define the optimal device in this clinical setting, the results of this prospective, non-randomised study support the wider use of TIAP in oncology patients undergoing HDCT and autologous stem cells transplantation.

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References


