Eur J Cancer Clin Oncol, Vol. 25, No. 6, pp. 939–944, 1989.
Printed in Great Britain

0277-5379/89$3.00 + 0.00

Classical External Indwelling Central Venous Catheter Versus Totally Implanted Venous Access Systems for Chemotherapy Administration: a Randomized Trial in 100 Patients with Solid Tumors

P. CARDE, M.F. COSSET-DELAIGUE, A. LAPLANCHE and I. CHAREAU
Institut Gustave-Roussy, 39, rue Camille-Desmoulins, 94805 Villejuif Cedex, France

Abstract—*A prospective randomized trial was organized at the Institut Gustave-Roussy to assess the reliability of classical external catheters (CE) versus totally implanted access systems (TI) for delivering intravenous chemotherapy for a duration of at least 6 months. The analysis was performed on the 96 patients whose implantation succeeded (CE 46, TI 50). Failure was defined as loss of ability to function (followed by removal) within the 6-month period of the survey. Patients dying with functional catheters were considered as censored (15 cases) at the time of death. Twenty-four access systems were removed. The removal-free curves differ significantly ($P < 0.001$), favoring the TI access systems. The main reasons for removal were: catheter fall (CE 6, TI 0), migration (CE 1, TI 1), infection (CE 5, TI 1), thrombotic occlusion (CE 1, TI 0) and venous complications (CE 1 thrombosis plus 1 pulmonary embolism, TI 1 thrombosis). In addition, a survey by questionnaire demonstrated a significantly better patient activity rate ($P = 0.02$) and hygiene ($P < 0.001$) in the TI group. This prospective randomized study demonstrates that totally implanted access systems are more reliable, safer and better tolerated than classical external catheters for solid tumor patients undergoing intravenous chemotherapy for longer than 6 months.*

INTRODUCTION

SUSTAINED vascular access has been a persistent problem in patients receiving chemotherapy involving irritating and ulcerating drugs over months or years. Complications related to drug administration include local inflammation, drug infiltration (with subsequent necrosis and ulceration), local infection and septicemia, as well as increased patient aversion to chemotherapy. Indwelling central venous catheters have become the most common way to deal with these problems and much has been written about their safety and risks [1–3]. More recently, totally implanted central venous access systems have been tested. These require no dressing changes or heparin flushes between uses [4, 5]. However, local and catheter infection does occur, as well as thrombotic complications, although at variable reported rates [2, 6]. To date, there has been no suitable comparison between classical external and totally implanted access systems; hence, the advantages and disadvantages of each system remain unevaluated. A randomized trial was therefore performed at the Institut Gustave-Roussy to compare classical external catheters with totally implanted systems with regard to duration of use, complications and convenience.

MATERIALS AND METHODS

All patients who had malignancies which would require intravenous chemotherapy for more than 6 months, and who had either poor or no peripheral access, or wished to be placed on central venous access from the onset of chemotherapy were eligible for the study. These adult patients were informed about the protocol before giving consent. Patients whose disease characteristics or previous history could interfere with compliance to the protocol were excluded: HEENT and upper thorax located malignancies; cutaneous infection at the planned insertion site; prior thrombo-embolic disease; unreliability for follow-up and maintenance of the implants; significant aplasia, either expected or

Accepted 7 December 1988.
Supported in part by a grant from ARC (Association pour la Recherche sur le Cancer), 16 Avenue Paul Vaillant Couturier, BP 3, 94801 Villejuif Cedex, France.

present, due to treatment intensity; life or treatment duration expectancy less than 6 months. Eligible patients were assigned to the classical external catheter or totally implanted system groups by balanced randomization of every six subjects. The silicone catheter (Nutricath 'S', Vygon, France; inner diameter 1–2 mm; outer diameter 2 mm) was implanted, using local anesthesia, with a siliconized peel-away introducer to thread the catheter into the superior vena cava/right atrium (Désilet 1129, Vygon, France). The catheter was tunneled subcutaneously and its position was confirmed by chest X-ray. The implanted system (Port-a-Cath, Pharmacia, France) consisted of a stainless steel disc with a silicon rubber septum and dead space of 0.4 ml connected to a silastic catheter (inner diameter 1.02 mm; outer diameter 2.8 mm), using a slip ring. It was implanted under general or local anesthesia. Following catheter placement, a subcutaneous tunnel was made and the catheter connected to the port placed in a pocket created in the subcutaneous tissue of the infraclavicular fossa. For the classical external CE catheter as well as for the totally implanted TI access systems the overwhelming majority of implantations were entirely performed by the anesthetist who took care of the entire procedure. For injection into the port, special needles with side-wall opening were used to preserve septum integrity. The systems were used for intermittent bolus or prolonged drug injections but not for protracted drug infusions in out-patients. All types of chemotherapeutic drugs were used, including Adriamycin®, *cis*-platinum, high dose methotrexate and cytosine–arabinoside. Patient progress was followed at least until the time of evaluation, 6 months from the date of implantation. Success was defined in terms of the ability to use the same venous access for at least 6 months. Therefore, failure was defined as the necessary removal of the device, for various reasons (e.g. complication, patient refusal) during the 6-month follow-up period. Patients who died or were lost to follow-up were removed from consideration (i.e. as having a functional venous access at death or at last consultation) for statistical analysis. The functional duration of the material was defined as the period between implantation and date of failure, death or last consultation. Complications were assessed at each course of chemotherapy.

It was estimated that 50 subjects per group would be adequate to demonstrate a 35% difference between the success rate in each of the two groups, whatever the 6-month success rate would be (type I error = type II error = 5%). Percentages were compared by the chi-square test. Cumulative success rates were estimated by the Kaplain–Meier method [8]. Confidence intervals were calculated by the Rothman method [9]. Cumulative success rate curves were compared by the log-rank test [10]

RESULTS

Completion of the trial

One hundred and six subjects entered the trial over a period of time lasting for 13 months. It was only 6 months after the last patient entered the trial that the analysis was performed. Of these patients, six were rejected (three in each treatment group) prior to the implant insertion, due to early deaths (2), eventual patient refusal (1), cerebral metastasis (1), phlebitis (1) and double inclusion (1). Thus, the analysis was based on 100 patients (50 CE and 50 TI accesses). Table 1 shows the distribution of patients according to the type of cancer. The percentage of women (86% and 80%, respectively) and mean ages (48.5 years and 49.1 years) did not differ significantly between the two groups, CE and TI respectively.

Insertion of the material

The mean interval between randomization and implant insertion was 10 and 14 days in the CE and TI groups respectively (NS). General anesthesia was used for 10 TI insertions but not for CE insertion ($P < 0.001$). The mean duration of the procedures were 28 and 60 min ($P < 0.001$) for CE and TI insertions respectively. This insertion required the presence of one or two anesthetists and of one or two dressing nurses: only one anesthetist in 47 CE and 35 TI insertion cases ($P = 0.02$), only one dressing nurse in 49 CE and two TI insertions ($P < 0.001$); a surgeon was required only once for a TI placement. Table 2 shows the rate of success (92% and 100%, NS) and complications (20% and 16%, NS) observed in the CE and TI groups respectively as related to the placement procedure.

Chemotherapy administration

The mean interval between implant insertion and the first course of chemotherapy was 6 and 3 days in the CE and TI groups respectively (NS). Both

Table 1. Distribution of tumor types for each of the venous access systems

Tumor type	Classical external access ($n = 50$)	Totally implanted access ($n = 50$)
Breast	23	17
Ovary	10	8
Uterus–vagina	4	4
Testis–bladder	6	5
Gastro-intestinal	2	4
Soft tissue sarcoma	2	4
Hodgkin's disease	1	1
Non-Hodgkin's lymphoma	1	0
Miscellaneous	1	4
Unknown primary	0	3

Table 2. Distribution of failures of implantation and related complications for each of the venous access systems*

Implantation	Classical external access (n = 50)	Totally implanted access (n = 50)
Failures	4	0
Complications	10	8†
Pneumothorax	(2)	(2)
Hematoma	(2)	(2)
Hemorrhage	(0)	(1)
Catheter malposition‡	(3)	(3)
Miscellaneous	(3)	(1)

*There were no implantation-related fatalities.
†One patient had two complications.
‡Ultimately corrected.

types of catheters were used both for drawing blood and for drug administration. No attempt at blood transfusion was made in the TI group. The devices were used three to five times in each chemotherapy course. The mean number of chemotherapy courses administered through the access systems was four and five respectively for the CE and TI groups ($P = 0.03$).

Catheter removal

Among the 96 patients whose implant insertion was successful, 15 deaths were observed during the 6-month follow-up period; seven from the group of CE patients and eight from the group of TI patients. The survival curves of the two groups do not differ. Of the 81 patients still alive 6 months after their inclusion, 24 intravenous access systems were removed during the follow-up period (20 of 39 patients in the CE group and four of 42 patients in the TI group). Considering subjects who died with a functional intravenous access system as censored data at the time of death, we estimated the removal-free curves on the two groups (Fig. 1). The curves significantly differ ($P < 0.001$). The removal rates observed during the 6-month follow-up period were

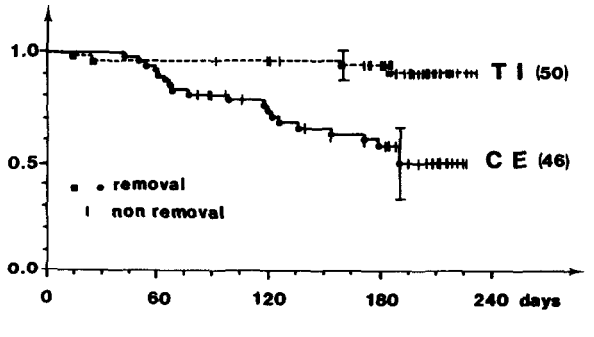

Fig. 1. Removal-free curves of catheters in the two groups, totally implanted catheters (TI) and classical external catheters (CE) (95% confidence intervals). Early censored data (15 patients) correspond to deaths from disease progression during treatment.

50% and 10% in the CE and TI groups, respectively. Table 3 shows the causes of catheter removal. In only one instance was a catheter migration observed in the TI group, whereas seven cases (fall or migration) were observed in the CE group. All infectious incidents were ultimately controlled by catheter removal and adapted or broad spectrum antibiotics.

In the CE group, five cases of infection led to catheter removal. In two instances, both ends of the catheters provided positive cultures of *Staphylococcus aureus*; two cases were recorded as septicemic syndrome with negative blood culture; the last case was local infection refractory to drainage and antibiotics.

Convenience

The patients' approval, the frequency of severe pain, aesthetic damage, restriction of physical or professional activity, effect on family life and personal hygiene were recorded. Patients approved of both intravenous access systems, but the restrictions on patient activity (CE 18%, TI 0%; $P = 0.02$) and on hygiene (CE 49%, TI 5%; $P < 0.001$) were fewer among totally implanted systems than among external catheters.

DISCUSSION

A randomized trial allowed us to assess the reliability of external catheters as compared to totally implanted accesses for patients undergoing a chemotherapy program of at least 6 months duration. The reliability of the catheter was higher in the TI group, where only four of 42 patients at risk had their access system removed during the 6 months, versus 20 of 39 patients with CE catheters.

Safety was also greater with TI access systems: catheter migration and infection were observed once each while they were observed in seven and five instances, respectively, in the CE group. The mean number of chemotherapy courses delivered was four with the CE and five with the TI access ($P = 0.03$). The TI access system also improved convenience for patients, both in terms of coping with normal activity ($P = 0.02$) and better hygiene ($P < 0.001$).

The need for reliable repeated venous access has been met these last few years by long-term percutaneous catheterization, which takes advantage of new silicone elastomer materials [1, 7, 11, 12]. Subcutaneous tunneling and the use of dacron-sheath incorporated catheters aim to reduce the 10–25% infection rate related to outside exit, frequent dressing changes and heparin solution flushes [1, 11]. These infections lead to catheter removal in more than 10% of the patients. It has been our experience that the infection rate was similar whether implantation was routinely performed surgically or by the anesthetic team. Initial experience with implantable port-catheter systems have been encouraging in terms of infection and

Table 3. Distribution of causes of removal for each of the venous acess systems

Reason for removal	Classical external access (n = 46*, 39†)	Totally implanted access (n = 50*, 42†)
Infection	5	1
(positive catheter cultures at both extremities)	(2)	(0)
(*Staphylococcus aureus* septicemia)	(0)	(1)
(septicemic syndrome with negative blood culture)	(2)	(0)
(local infection; negative catheter culture)	(1)	(0)
Thrombotic occlusion of catheter	1	0
Venous thrombosis	1	1
Pulmonary embolism	1	0
Catheter fall	6	0
Catheter migration	1	1
Lymphangitis	1	0
Catheter dislodgement	1	0
Unknown	1	0
End of chemotherapy	2	1

*Number of successfully implanted patients.
†Number of patients at risk for 6 months (seven and eight deaths, respectively, occurred during the interval).

occlusion rates [4, 5]. This also has been our experience both for intravenous [13, 14] and intraarterial catheterization [15]. However, the broad range of complications reported for both means of venous access, probably related to experience and patient recruitment at different centers, precluded defining a standard choice approach with possible financial implications unless quantitative data could be obtained from a homogeneous group of patients. This led to the present randomized trial.

The catheter withdrawal-associated infection rate in the CE group (five out of 39 patients at risk for 6 months, 12%) was as expected from the literature using standard Hickman–Hroviac catheters [1, 11, 12]. However, the infection rate in the TI group (one of 40 patients = 2.5%) is definitely lower and similar to the range reported elsewhere [3–5, 11, 14]. These results, from a prospective randomized trial, support a retrospective comparison [16], made in superimposable patient groups between 110 patients who had placement of a Broviac catheter and 100 who had a TI access, which also yielded a significantly different catheter related sepsis rate (15% and 3%, respectively).

Also, this retrospective comparison [16] favored the use of TI access for thrombotic occlusions (22% versus 1%), as have other reports [3–5, 11, 14]. In our prospective trial, heparinized serum washings, in some instances with the help of urokinase [17], usually succeeded in reestablishing the catheter permeability in both arms. However, these maneuvers did not succeed in one instance (one thrombotic occlusion in 39 patients with CE catheters).

Nevertheless, our trial also supported the superiority of TI access in term of venous complications (one venous thrombosis in 42 patients with TI catheters versus one venous thrombosis plus one pulmonary embolism in 39 patients with CE catheters). Veinography has been used to obviate subclavian vein occlusion and collateral flow around the catheter [6] in a few cases suspected of insidiously developing occlusions (poorly defined chest wall, scapular or neck pain, no blood withdrawal possible) which could lead to drug extravasation [6].

TI access systems were also found to be clearly superior with respect to the issue of accidental removal (CE 6/39 versus TI 0/42). In addition, one case of catheter migration was observed in each group. The attachment of the catheter to the TI disc through a steel slip ring appeared to be much safer than the conventional maneuver of securing an external catheter to the skin. Miscellaneous causes of CE access withdrawal were also more numerous (lymphangitis one, catheter malposition one). Finally, the curves of removal events significantly differed ($P < 0.001$) due to the previously detailed four factors.

The major questions in the scope of this study have been answered for only this homogeneous patient group (patients with predominantly solid

tumors undergoing intermittent non-aplastic chemotherapy for a minimum 6-month period) in well-defined technical conditions with non-surgical implantations, performed by a trained specialized team since 85% of all patients were managed by one of us (M.F.C.). The conclusions of the study may not be valid for other situations, such as chemotherapy regimens with protracted continuous infusions [6] or prolonged aplastic episodes requiring frequent blood transfusions and extensive parenteral nutrition. The inner diameter of catheters attached to the TI systems did not allow such comparative study at the time this study was initiated. Conversely, in patients undergoing chemotherapy or neoadjuvant chemotherapy for short durations, the superiority of the TI access systems seen above may not counterbalance the inconveniences of its initial cost and of its requirement for expert positioning. Indeed even difficult peripheral infusions or repeated CE positioning may be preferred in case of treatment predicted to be short. We failed to assess accurately the relative costs of the two procedures: it was predicted that the cost of the devices would represent most of the costs. Actually, maintenance costs have been far more important in the CE access arm. However, cost assessment was not feasible in such a prepaid financial system as ours.

In our experience, chemotherapy delivery has been improved by using TI access systems, as demonstrated when access removal curves are compared for infectious events, thrombosis and catheter fall or migration. Moreover, easier physical activity and hygiene care also favor TI accesses, as claimed by patients undergoing chemotherapy. In spite of higher initial purchase and insertion prices (type of anesthesia, hospitalization, duration and staff involved for the implantation procedure) final costs are also lower for the TI accesses. When new TI devices become available, particularly with larger inner diameters for catheters and needle gauge, more extended use, mainly for aplastic patients who need blood derivative transfusions and parenteral nutrition, may be possible.

Acknowledgements—We thank C. Paoletti for data collection. We are indebted to Dr J.L. Amiel, Dr M. Benahmed, Dr B. Callet, Dr J.P. Droz, Dr B. Escudier, Dr M. George, Dr S. Hane, Dr C. Kalifa, Dr F. May-Levin, Dr E. Richard, Dr J. Rouesse, Dr P. Rougier, Dr J. Ruffie, Dr J.L. Wendling for their contributions to the data; to C. Pieddeloup and H. Sancho-Garnier for their participation to the establishment of the statistical protocol; to C. Chimchirian for the preparation of this manuscript.

REFERENCES

1. Hickman RO, Buckner CD, Clift RA, Sanders JE, Stewart P, Thomas ED. A modified right atrial catheter for access to the venous system in marrow transplant recipients. *Surg Gynecol Obstet* 1979, **148**, 871–875.
2. Bothe A, Piccione W, Ambrosino J, Benotti PN, Lokich JJ. Implantable central venous access system. *Am J Surg* 1984, **147**, 565–569.
3. Meurette J, Delpadt G, Meynadier J. Vascular access for intravenous chemotherapy: totally implanted systems. *Eur J Surg Oncol* 1985, **11**, 295–298.
4. Gyves J, Ensminger W, Niederhuber J *et al.* Totally implanted system for intravenous chemotherapy in patients with cancer. *Am J Med* 1982, **73**, 841–845.
5. Gyves J, Ensminger W, Niederhuber J *et al.* A totally implanted injection port system for blood sampling and chemotherapy administration. *JAMA* 1984, **251**, 2538–2541.
6. Lokich JJ, Bothe A Jr, Benotti P, Moore C. Complications and management of implanted venous access catheters. *J Clin Oncol* 1985 **3**, 710–717.
7. Broviac JW, Cole JJ, Scribner BM. A silicone rubber atrial catheter for prolonged parenteral alimentation. *Surg Gynecol Obstet* 1973, **136**, 602–606.
8. Kaplan EL, Meier P. Non parametric estimations from incomplete observations. *J Am Stat Assoc* 1958, **53**, 457–481.
9. Rothman KJ. Estimation of confidence limits for the cumulative probability of survival in life table analysis. *J Chron Dis* 1978, **31**, 557–560.
10. Peto R, Pike MC, Armitage P *et al.* Design and analysis of randomised clinical trials requiring prolonged observations of each patient. II analysis and examples. *Br J Cancer* 1977, **35**, 1–39.
11. Wade JC, Newman KA, Schimpff SC *et al.* Two methods for improved venous access in acute leukemia patients. *JAMA* 1981, **246**, 140–144.
12. Reed WP, Newman KA, de Jongh C *et al.* Prolonged venous access for chemotherapy by means of Hickman catheter. *Cancer* 1983, **52**, 185–192.
13. Pichard E, Deruennes E, Lebland A, Pico J, Truffa-Bachi J. L'abord veineux central en oncologie et hématologie pédiatrique. *Cah Anesthesiol* 1983, **31**, 651–656.
14. Champault G, Faure P, Carde P, Patel P, Boutelier PH. Pose chirurgicale et utilisation des cathéters implantables: 260 cas. *Actualités chirurgicales 86ème Congrès français de chirurgie.* Paris, Masson, 1984.
15. Elias D, Rougier P, Lasser P, Droz JP. Chimiothérapie intraartérielle discontinue et ambulatoire par l'intermédiaire d'une chambre d'accès sous-cutanée dans le traitement des métastases hépatiques isolées. *Ann Gastroenterol Hepatol* 1985, **21**, 95–97.

16. Greene FL, Moore W, Strickland G, McFarland J. Comparison of a totally implantable device for chemotherapy (Port-a-Cath) versus longterm percutaneous catheterization (Broviac). *Proc ASCO* 1986, **5**, 245.
17. Fraschini G, Jadeja J, Lawson M, Holmes FA, Carrasco HC, Wallace S. Local infusion of urokinase for the lysis of thrombosis associated with permanent central venous catheters in cancer patient. *J Clin Oncol* 1987, **5**, 672–678.