Eur J Cancer, Vol. 27, No. 2, pp. 147–149, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Continuous Infusion of Chemotherapy on an Outpatient Basis via a Totally Implanted Venous Access Port

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170 patients were treated with continuous infusion of epirubicin, mitoxantrone, carboplatin or 5-fluorouracil through an implanted venous access port with a portable infusion pump. A total of 440 cycles were given on an outpatient basis. The patients were instructed how to dissolve their drugs and to change the syringes. The complication rate was low. 10 patients developed a thrombosis of the subclavian vein, resulting in cessation of therapy in 5. Pulmonary embolism occurred twice, in 1 patient during a period of subclavian vein thrombosis. Needle dislocation occurred 6 times and catheter occlusion 20 times. Patency was restored with saline or urokinase. Local infection occurred 3 times and systemic infection only once. This technique is suitable for continuous infusion of different cytostatic drugs on an outpatient basis. Patients were able to prepare their drugs at home and the system can remain *in situ* for 3 weeks without increasing the complication rate.
Eur J Cancer, Vol. 27, No. 2, pp. 147–149, 1991.

INTRODUCTION

SUBCUTANEOUS IMPLANTATION of an intravenous access port with a portable infusion pump means that cancer patients can receive continuous infusions as outpatients. Several groups have described their experience with different catheters, infusion pumps and chemotherapy regimens [1–3]. However, there is no consensus on the most suitable catheter for long-term use on an outpatient basis.

For eight phase I and II studies we chose one specific implantable venous access device combined with one portable pump for administration of epirubicin [4–6], mitoxantrone [7, 8], carboplatin [9] or 5-fluorouracil (5-FU) [10] in a continuous schedule over several weeks. Patients were treated on an outpatient basis and in seven of the eight studies they were instructed how to prepare their drugs [11]. We report our experience with continuous infusion in these 170 patients.

PATIENTS AND METHODS

The patients participated in one of the eight studies (Table 1). Only patients who were willing to take an active part in an investigational study were accepted after informed consent was obtained. Epirubicin, mitoxantrone and carboplatin were administered in cycles of 3 weeks followed by a 3 week rest; 5-FU was given in cycles of 2 weeks followed by a 2 week rest. The patients were admitted for insertion of the implantable venous access port (Infuse-A-Port). The implantation was done under local anaesthesia, preferably on the left side. In patients with tumour or previous surgery or radiotherapy of the left chest wall or jugular region, the right side was chosen. A 22 G 90° bent Huber-point needle of 19 or 32 mm was connected to a Luer-Lock extension tube (Vygon Lectrocath). The needle was secured on the skin with Steri-strips and a sterile transparent plastic dressing (Tegaderm, 10 × 11 cm, or, in cases with local allergy, Opsite 10 × 14 cm). At the end of each cycle the port was flushed with 10 ml heparinised saline (50 U/ml). Between courses the system was not flushed. When obstructed, the catheter was flushed with normal or heparinised saline or with 5000 U urokinase.

The Graseby Medical MS 16A syringe driver was worn in a cotton shoulder holster. This is a battery-powered pump. Pumps were adjusted to a specific infusion rate and the patients changed the syringe every 12, 24 or 48 h.

During their stay in hospital for port implantation, patients were instructed by the oncology nurse on how to prepare their cytostatic drugs. In one phase II study with epirubicin the hospital pharmacy delivered, ready for use, plastic-wrapped sterile syringes. The patients also learned how to change the syringe and manage the syringe driver. The patient was dis-

Table 1. Phase I–II studies with continuous infusion via implantable venous access port

Phase/drug	No. of patients	No. of courses (range)	No. of days (range)
I/epirubicin	23	56 (1–12)	1176 (7–168)
II (colorectal)/epirubicin	14	32 (1–3)	672 (14–42)
II (gastric)/epirubicin	33	83 (1–12)	1753 (7–168)
I/mitoxantrone	25	50 (1–3)	1050 (21–63)
II (breast)/mitoxantrone	10	47 (2–6)	658 (28–84)
I/carboplatin	44	101 (1–9)	2121 (21–189)
II/5-FU (colorectal)	13	57 (1–8)	822 (14–112)
II/5-FU + alpha interferon	8	14 (1–2)	185 (12–28)
Total	170	440	8437

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Revised 5 Nov. 1990; accepted 16 Nov. 1990.

charged when deemed capable of preparing the drugs. Further treatment was as an outpatient. The responsible doctor could always be reached. In the first studies, the patients were seen once weekly. Since the complication rate was low in these trials, we decided to leave the needle *in situ* for 2–3 weeks in the next studies. Diluent and drugs were dispensed for 1 or more weeks, depending on the stability of the drug used. Courses were continued if toxicity, tumour progression and complications were absent. Anticoagulant or antibiotic prophylaxis was not given routinely. The port was never used for blood sampling.

RESULTS

170 patients, 109 male and 61 female, with a mean age of 52 years (range 21–72), completed a total of 440 treatment cycles comprising 8437 infusion days (Table 1). Each patient received at least one complete cycle of 14 or 21 days, except for 2 patients who developed a thrombosis of the subclavian vein during the first courses which prevented further infusion. All patients were treated as outpatients and all patients who entered the study proved to be capable of preparing their drugs. A 3–5 day admission for implantation of the venous access port and instruction was sufficient in most patients. 1–9 cycles were given.

In most patients (165) infusion was stopped for tumour progression. A small number of complications were seen; most were easily managed. In 5 out of 10 patients with subclavian vein thrombosis infusion had to be stopped. In 1, a patient with previous mediastinal irradiation, vena cava obstruction recurred, despite initial resolvement by urokinase. The catheter was removed after a second urokinase infusion. In the other 5 patients (3 with breast carcinoma treated with mitoxantrone), axillary thrombosis did not preclude further treatment. 1 of these patients developed pulmonary embolism and obstruction of the superior caval vein. With anticoagulant therapy she reached a partial remission after 6 cycles. Another patient with breast carcinoma, also treated with mitoxantrone, developed pulmonary embolism without apparent thrombosis.

Temporary catheter occlusions required urokinase in 5 of 20 occasions. Usually, flushing with normal saline or heparinised saline cleared the block, without causing treatment delay. Drug extravasation from a dislodged needle occurred six times, without causing infection or tissue necrosis. Chemotherapy was never stopped for more than a week. Local infections of the skin were seen in 3 patients. 1 patient had a concomitant cryptogenic sepsis, which reacted well to antibiotic therapy. Pump failure occurred ten times due to mechanical dysfunction, wrong placing of the syringe or a flat battery. Repeated bending resulted in 20 fractures of the external catheter at the connection with the syringe, mostly after the system was used for longer than a week. Fractures of the internal catheter did not occur in this group of patients [12].

The nurses and doctors were impressed by the influence of this programme on the participation of the patients and their partners, who became more assertive and positive about the active role in their treatment [11, 13].

DISCUSSION

Many groups have described their experience with totally implanted venous access ports for a variety of agents [1–3, 13–16]. Compared with percutaneous central venous catheters, implanted venous access devices have several advantages. The lack of an external component reduces the risk of infection and septicaemia, and frequent manipulation for heparinisation is unnecessary [1–3]. The catheter is flushed with heparin at the end of each treatment course. In the period between use no special care is needed, nor are there limitations to the patients' daily activities. Cosmetically the venous access port is more acceptable for the patient. On the other hand, the subcutaneous needle carries the risk of drug extravasation. In our study, needle dislocation was seen in 6 out of 440 treatment courses, but was never accompanied by skin or deep tissue necrosis. Dislocation of the needle can be avoided by adequate fixation. A longer needle should be used in obese patients or in women with large breasts.

For the occurrence of venous thrombosis, Lokich *et al.* [1] reported subclavian vein thrombosis in 16% of 92 patients receiving chemotherapy or hyperalimentation by a totally implanted venous access system, while the rate of thrombosis with open-ended percutaneous catheters varied from 0 to 40% [1]. The frequency of venous thrombosis in more recent studies of implanted venous access ports for chemotherapeutic agents in different treatment schedules varied from 2 to 6% [1–3, 14–16]. This is similar to our data, in which subclavian vein thrombosis occurred in 10 patients (5%). No relation between the original diagnosis and the occurrence of venous thrombosis has been reported. In our series of breast carcinoma patients treated with mitoxantrone there was a higher frequency of thrombo-embolic complications than in the other treatment group ($P < 0.0005$) [7].

The external diameter of the catheter we used was 2.3 mm, which may be advantageous because the risk of thrombosis is correlated with an external diameter over 2.8 mm [1]. Catheter occlusion may be related to the internal diameter, occurring more often with a lumen over 0.51 mm [3, 14]. In our study with a catheter with a 0.63 mm lumen, no irreversible occlusion occurred.

The infectious complications comprised three local and one systemic infection, the latter probably from a different primary locus. This rate confirms the results of other groups [3, 15]. Contrary to earlier reports, central venous catheters do not have to be removed at the first sign of infection, which was never necessary in our series. Although all the regimens in our study were given on an outpatient basis, the infection rate was similar to that in inpatient schedules [3, 14, 15]. Brothers *et al.* [16] reported no increase in complications in an outpatient setting compared with inpatient treatment.

Pump failures never lasted more than 24 h and were never a problem. In comparison with other pumps for continuous infusion, our portable pump is easy to manage [13]. The syringe can be visually checked and easily changed. Furthermore, the pump is not too expensive and can be used by several patients.

During palliative treatment, chemotherapy regimens should aim at the least interference with a patient's daily activities. Continuous infusion of chemotherapy on an outpatient basis can certainly contribute to this. When patients can prepare their own drug, limited stability of a drug is no contraindication. Continuous infusion in an outpatient setting appears to be safe and reliable, which in our experience had a positive influence on the patients' wellbeing and feeling of commitment [11].

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Eur J Cancer, Vol. 27, No. 2, pp. 149–154, 1991.
Printed in Great Britain

0277-5379/91 $3.00 + 0.00

Factors Influencing the Establishment of Tumour-infiltrating Lymphocyte Cultures from Human Breast Carcinoma and Colon Carcinoma Tissue

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Tumour-infiltrating lymphocytes (TIL) were obtained from breast and colon tumour tissue and cultured *in vitro* in the presence of recombinant human interleukin-2. Seven of 35 breast tumours and five of 41 colon TIL cultures were established *in vitro*: proliferation rates of greater than 10^3 were achieved. The cytotoxic capacity of these cells was determined against the cell lines K562 and SW742, and percentage cytotoxicity levels of greater than 97% and 79%, respectively, were seen. An inverse relationship between the ability of TIL to kill and their proliferative capacity was observed in all cultures. The prominant phenotype was CD3 positive, with greater than 55% of TIL expressing this antigen; there was no expression of CD16. The expression of CD56 and CD25 varied, being maximumly expressed on 64% and 38% of TIL, respectively. When greater then 90% of TIL expressed CD3, the ability of the culture to kill the target cell lines was low; only when there was an increase in the proportion of cells expressing CD56 and a decrease in the expression of CD3 was there high cytotoxicity. This study indicates that the TIL which proliferate *in vitro* in the presence of interleukin-2 are not necessarily the mediators of cytotoxicity.
Eur J Cancer, Vol. 27, No. 2, pp. 149–154, 1991.

INTRODUCTION

THE STIMULATION of peripheral blood mononuclear cells (PBMC) with recombinant human interleukin-2 (rhIL-2) results in the appearance of lymphokine activated killer (LAK) cells capable of mediating non-MHC restricted cytotoxicity [1, 2]. These cells have been shown mainly to be CD3-negative, CD16-positive effectors, derived from large granular lymphocytes (LGL) or natural killer (NK) cells, together with a minor population of CD3 positive, CD16 positive/negative cells also possessing MHC unrestricted cytotoxicity [3]. Adoptive immunotherapeutic treatment of cancers using LAK effector cells and rhIL-2 has been undertaken, and the results show limited antitumour activity in patients with malignant melanoma, renal cell and colorectal carcinoma, giving clinical response rates of 35%, 21% and 17% respectively [4]: LAK cells in combination with rhIL-2 have not proved beneficial in the treatment of other human solid malignancies.

In an attempt to improve the clinical response of cancer patients to immunotherapy, lymphocytes isolated from the tumour mass, termed tumour infiltrating lymphocytes (TIL), have been assessed for the ability to promote tumour regression. Preliminary work in murine systems indicated that these cells