Reg Cancer Treat (1988) 1: 102–107

Regional Cancer Treatment

© Springer-Verlag 1988

Original article

Intra-arterial infusion chemotherapy for recurrent breast cancer via an implantable system*

K.R. Aigner, H. Walther, H. Müller, J. Jansa and N. Thiem*****

Department of General and Oncologic Surgery, Trostberg Hospital, D-8223 Trostberg, Federal Republic of Germany

Abstract. A new technique of cytotoxic subclavian artery infusion via an implantable port catheter (Pulmoplant, and Implantofix-select B. Braun, Melsungen, FRG) has been applied in 39 patients suffering from recurrent breast cancer. Patients received at least four cycles of MMC/5-FU/folinic acid by intra-arterial infusion. The overall response rate was 92%: 31% CR, 41% PR, and 20% MR. No change was noted in 5%, no response in 3%. Patients without previous treatment had 42% CR and 42% PR, while patients with prior chemotherapy and radiotherapy had 15% CR and 46% PR. Subclavian artery infusion is tolerated well and the quality of life is improved.

Key words: Intra-arterial infusion chemotherapy – recurrent breast cancer – Implantable port catheter

Introduction

Recurrent breast cancer is known to be rather resistant to therapy: first, patients may have had prior cumulative doses of systemic chemotherapy with poor response, and second, recurrence is often located in or around a previously irradiated area. The only therapeutic alternative, if any, has been invasive surgery involving transposition of muscular or omental flaps, offering little chance of cure in a tumor whose biological behavior, i.e., its pattern of dissemination, is unpredictable.

Treatment regimens with high-dose locoregional chemotherapy have recently been tested [4, 6], with impressive results. The catheter techniques described herein have been developed recently [1] by our group.

Patients and methods

Catheterization techniques

A new technique for subclavian artery cannulation, including three variations has been developed. We usually apply a Pulmoplant or Implantofix-Select catheter shown in Fig. 1 (B. Braun, Melsungen, FRG), which is inserted with or without a retention rim at the tip, depending on the technique and on the site of vascular access (Fig. 2). We generally aim at infusing the whole subclavian artery with all its side branches in order to achieve homogeneous distribution of the cytotoxics all over the chest wall, shoulder and neck.

Catheterization via the axillary artery, the most commonly used technique, is generally performed at the end of an axillary dissection for staging or removal of lymph node metastases. The artery is exposed amidst the nerve plexus and secured with a tape. The free rimless tip of a Pulmoplant catheter is then inserted through a stitch and loosely fixed with a 5.0 prolene purse-string suture

Fig. 1. Implantofix-select (B. Braun) catheter, a modified version of the Pulmoplant

Fig. 2. Incisions for subclavian artery cannulation: *1*, axillary access; *2a*, lateral infraclavicular access; *2b*, medial supraclavicular access

Fig. 3. Placement of Pulmoplant axillary catheter

Fig. 4. Positioning of subclavian artery catheters: *1*, aorta; *2*, brachiocephalic trunk; *3*, carotid artery; *4*, subclavian artery, *5*, Pulmoplant with rim tip; *6*, Pulmoplant without retention rim

Fig. 5. End-to-side implantation of Implantofix-Select catheter with rim tip

Fig. 6. Blue coloration of chest wall after injection of blue dye through subclavian Pulmoplant catheter

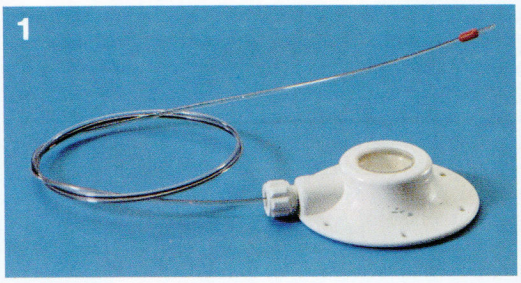
Fig. 8. Postradiation local recurrence before **(a)** and after **(b)** regional chemotherapy

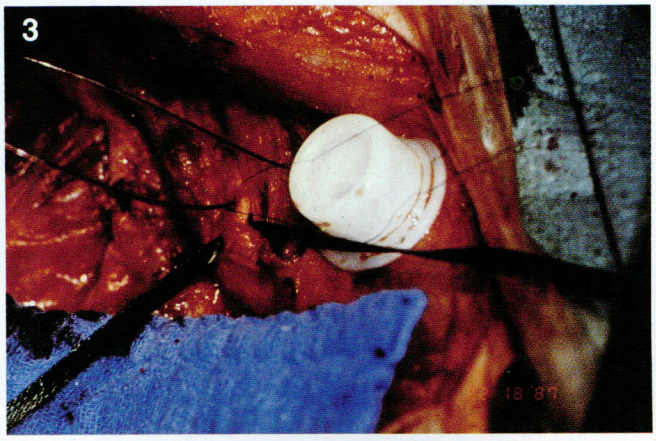
* This study was supported by Medac, Hamburg, FRG

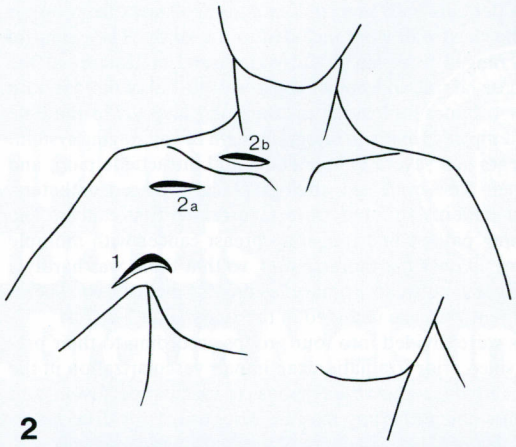
** Gynecologist, Marienstrasse 3, D-8220 Traunstein, FRG

*** Substantial portions of the data published here are from the thesis of N. Thiem

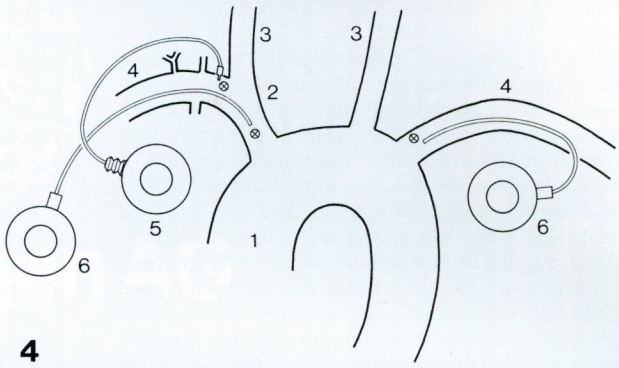
Offprint requests to: K.R. Aigner



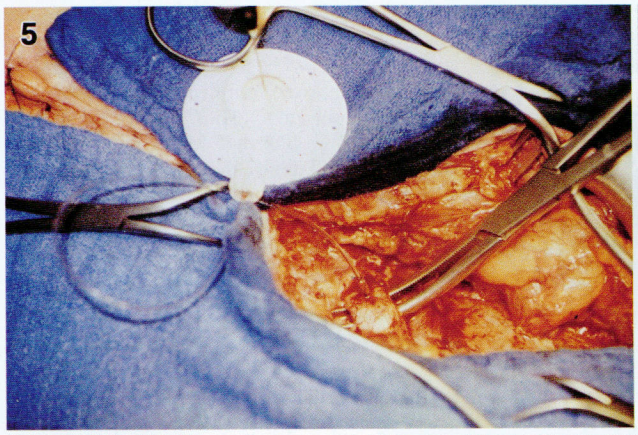


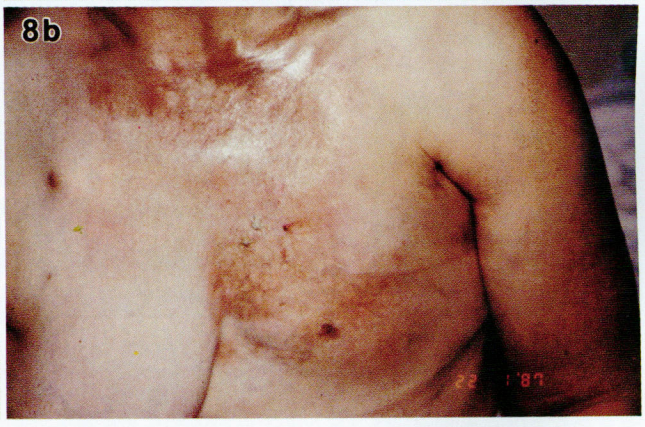


2



4





(Fig. 3) in such a way that it can still be slipped to and fro. Under X-ray control with contrast medium the tip of the catheter is then advanced to its final position. On the left side the technique is easy, since the tip can be positioned directly behind the origin of the subclavian artery from the aortic arch (Fig. 4) and the port placed in an infraclavicular subcutaneous pouch. Care must be taken not to infuse the aortic arch. On the right side the tip of the catheter is either placed between the vertebral artery and the common carotid artery or advanced further into the brachiocephalic trunk.

Catheterization of the subclavian artery can be performed via either of approaches (Fig. 2), the lateral infraclavicular or the medial supraclavicular.

The lateral infraclavicular approach begins with an incision from the deltopectoral groove toward the median part of the clavicle. The subclavian artery is exposed and secured with a tape. Via an incision through a 5.0 prolene purse-string suture the catheter is inserted in the same manner as in the axillary approach. Exact positioning of the tip under X-ray control is the same as described above.

The advantage of this technique over the axillary technique is a shorter free distance of the catheter within the vessel and therefore a decreased risk of thrombosis. An even more important advantage is the absence of a nerve plexus in this area. Thus mechanical irritation of nerves, either by the catheter itself or through induction of connective tissue growth is avoided.

The medial supraclavicular approach is normally employed only on the right side, where topographically it is easy because of the common origin of the carotid and the subclavian artery from the brachiocephalic trunk. On the left side this approach is used only in those caser where the lateral approach is not viable because of extensive scarring, previous irradiation, or the risk of wound infection. An incision is performed from the right edge of the jugulum, parallel to the clavicle. First the internal jugular vein and common carotid artery are exposed. Along the carotid artery caudally the brachiocephalic bifurcation is identified. By means of this the right subclavian artery is localized and exposed. The catheter used in this site is implanted in end-to-side technique. Therefore it has to be armed with a retention rim which serves to fix the tip by means of a prolene purse string (Fig. 5). An Implantofix valve tip catheter designed for use in babies can be employed instead of a Pulmoplant open-end catheter.

Table 1. Prior treatment in patients receiving subclavian artery infusion chemotherapy for recurrent breast cancer

Group	Pretreatment	Number of patients
I	None	12/39
II	Irradiation	4/39
III	Chemotherapy	10/39
IV	Irradiation + chemotherapy	13/39

Table 2. Schedule (Trostberg) for subclavian artery infusion chemotherapy for recurrent breast cancer

Day	Drug	Total dose
1	MMC	14 mg
2	Folinic acid[a]/5-FU	50 mg / 1000 mg
3	Folinic acid[a]/5-FU	50 mg / 1000 mg
4	Folinic acid[a]/5-FU	50 mg / 1000 mg

[a] Rescuvolin C Medac, Hamburg, FRG

In most cases the correct position of the catheter can easily be checked by bolus infusion of blue dye (Indigocarmin) into the port. The entire chest wall turns blue from the neck downward along the midline of the sternum to 5–7 cm above the umbilicus (Fig. 6). Catheters need not be flushed with heparinized saline, except immediately after therapy. Care must be taken to withdraw the needle with the syringe under pressure, because otherwise blood might enter and clot the catheter. For prophylaxis of arterial thrombosis we administer two tablets of Asasantin daily. In large vessels with a high flow rate, low-dose aspirin (baby aspirin 100 mg daily) is sufficient.

Patients

Thirty-nine patients with recurrences and metastases from breast cancer at the chest wall were included in the study. The extent of the lesions ranged from small and widespread metastases at the ventral and/or lateral and dorsal chest wall to bulky disease with large tumor volumes infiltrating the muscular layers. For the time being no attempt was made to integrate them in any staging system. Three patients had severe lymphedema and intractable pain, and received their first cycle via angiographically placed catheters. Thirty-eight patients suffered from recurrent breast cancer. The one remaining patient had fungating breast cancer with multiple bulky lesions all over the thoracic wall, so that there was hardly a difference in size between primary lesion and metastases. Therefore this patient was also included in the study (Fig. 7 a, 7 b).

Patients were divided into four groups according to their pretreatment, since prior irradiation can impair vascularization in the tumor area and thus reduce the response to vascular perfusion, and prior systemic chemotherapy may be responsible for drug resistance (Table 1).

Chemotherapy

Subclavian artery infusion comprised four cycles at 4-week intervals. A cycle consisted of mitomycin C (MMC 14 mg) and folinic acid (50 mg)/5-fluorouracil (5-FU; 1000 mg). MMC and 5-FU were infused in 60 min, folinic acid in 5 min (Table 2). In case of recurrence 30 mg ADM infused in 60 min was added to the schedule. The maximum number of courses given to one patient was nine. Eleven patients received more than four courses.

Response criteria

Response was estimated almost exclusively according to clinical features and tumor markers. Macroscopic reduction in size by at least 50% was considered partial response (PR), reduction by between 30% and 50%, minor response (MR). Complete disappearance of all lesions was considered complete response (CR). In addition, tumor markers (CEA, CA 15-3) were measured. They were, however, not accorded the same importance as the macroscopic findings, because even in the case of a significant decrease of markers, any remaining slight elevation might be due to tumor in locations other than the chest wall. Tumor markers were checked routinely at 4-week intervals in order to detect any sudden changes. Clinical controls were carried out after four initial courses of therapy and repeated every 3 months.

Results

Response

There was an overall response rate of 92%, consisting of 31% CR, 41% PR, and 20% MR. No change (NC)

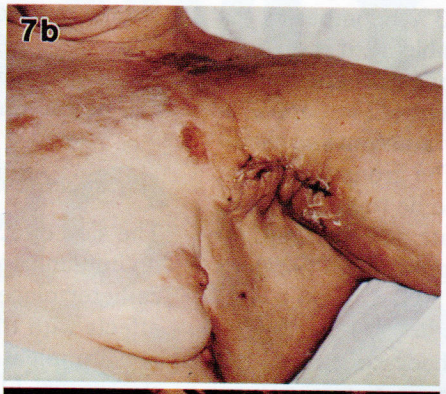


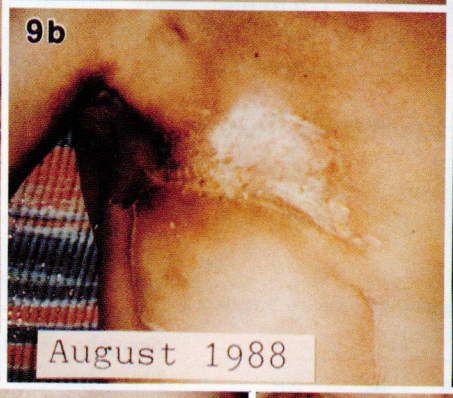
Fig. 7. Bulky chest wall metastases from breast cancer before **(a)** and after **(b)** regional chemotherapy

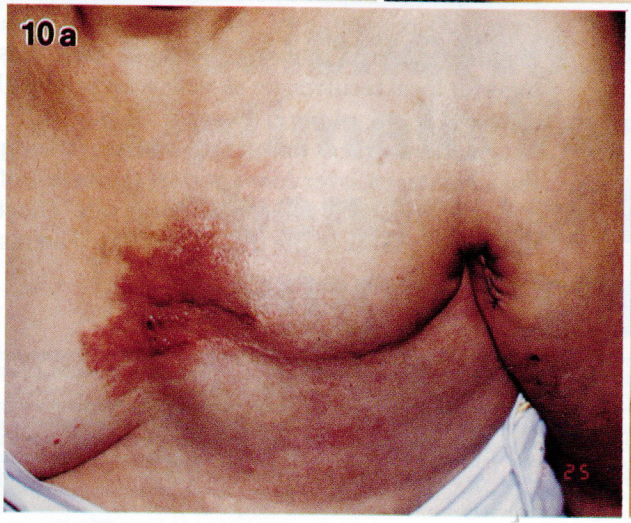
Fig. 9. Locally recurrent breast cancer before **(a)** and after **(b)** regional chemotherapy

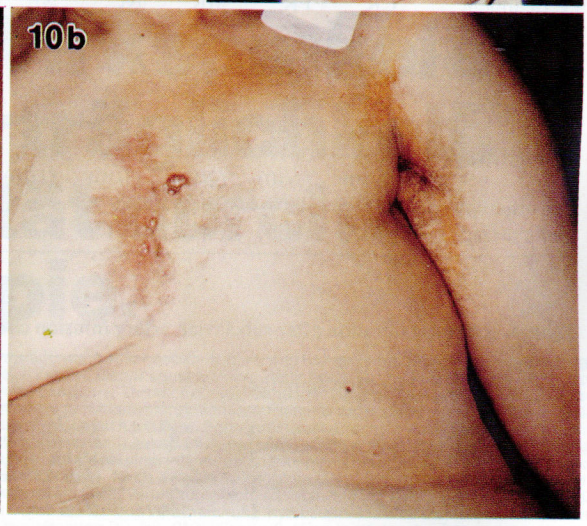
Fig. 10 a. Locally midline recurrence from breast cancer; **(b)** Same patient after left-side regional chemotherapy. Regression of left half of tumor due to high local drug tissue levels

Fig. 11. Local effect from "drug streaming"

Fig. 12. Hemialopecia from arterial infusion via the brachiocephalic trunk (patient had CR at the chest wall due to regional chemotherapy)







was noted in 5%, no response in 3%. Comparing the different pretreatment groups (Table 3), it is obvious that response rates are better among the patients who had received no previous treatment (42% CR, 42% PR) than in the group with prior irradiation and chemotherapy (15% CR, 46% PR). The group with prior irradiation is certainly too small to be representative, since there is a 50% (2/4) CR rate and a 50% (2/4) PR rate. Response rates in the group with previous chemotherapy are a little lower (30% CR, 30% PR) than in the nonpretreated group.

All three patients with lymphedema showed impressive remissions with decrease in tumor circumference and needed no more pain medication. Responders always showed a measurable response within 4–14 days after the end of the first course. It never happened that response occurred only after repeated courses with the same drug combination. If there is no immediate response, the schedule has to be changed.

Response durations are listed in Table 4. Nine of 12 patients in the CR group had disease-free intervals of between 7 and 14 months. Two suffered recurrence at 7, one at 8 and one at 11 months, and three patients were disease free at 12, 13, and 14 months. Up to the time of writing 75% of all treated patients were still without progression, so median relapse-free survival could not be calculated.

Two cases of CR are illustrated in Figs. 8 a, b and 9 a, b.

In one patient the dose-response behavior of breast cancer could be demonstrated in a chest wall recurrence located in the midline above the sternum (Fig. 10a). After one course of locoregional chemotherapy via the left subclavian artery, only the left half of the tumor disappeared (Fig. 10b).

Table 3. Response rates after regional chemotherapy according to pretreatment

Pretreatment	CR	PR	MR	NC	NR
None	42% (5/12)	42% (5/12)	17% (2/12)	–	–
Radiotherapy	50 (2/4)	50% (2/4)	–	–	–
Chemotherapy	30% (3/10)	30% (3/10)	20% (2/10)	10% (1/10)	10% (1/10)
Radiotherapy and chemotherapy	15% (2/13)	46% (6/13)	31% (4/13)	8% (1/13)	

Side effects and complications

The side effects are usually only moderate and have no influence on the patient's quality of life. Provided catheter placement is correct there are no local side effects with the drug schedule described above. The most unpleasant event that might occur is "drug streaming" [2, 5] due to lack of turbulence in the subclavian bloodstream, resulting in spot-like "skin burn" and soft tissue damage. This happened in two patients (Fig. 11). Hemialopecia on the right scalp (Fig. 12) from infusion of the carotid artery via the brachiocephalic trunk is not an unexpected side effect, but just a consequence of modified catheter placement in order to avoid drug streaming in nearby cervical or vertebral side branches. Thrombosis of the subclavian artery occured in one case where no aspirin prophylaxis was administered. Obviously there was sufficient time for development of collaterals, since the patient showed no clinical deficiences. Local wound infections were observed in three cases.

Discussion

Intra-arterial chemotherapy for advanced and fungating breast cancer has been described by some other groups in the past [3, 6]. Cannulation of the subclavian or mammary artery has usually been achieved by angiographic placement of catheters or by means of surgically placed catheters that were exited percutaneously. As described above, we have tried several techniques to implant permanent devices (Implantofix-select) consisting of thin catheters of adjustable length connected to ports. We have used these systems for local recurrences as well as for primary breast cancer [1].

At the thoracic wall, regional chemotherapy has the advantages, over conventional therapies, of a low complication rate, almost no local side effects and thus good quality of life during therapy. The response

Table 4. Response duration after subclavian artery infusion chemotherapy for recurrent breast cancer

Response	Duration (months)													
	1	2	3	4	5	6	7	8	9	11	12	13	14	34
CR	–	–	2[a]	–	1[a]	–	2	1	2[a]	1	1[a]	1[a]	1[a]	–
PR	2[a]	2[a]	1	2[a]	2[a]	1[a], 2	–	1[a]	–	1[a]	–	1[a]	–	1
MR	2[a]	–	1[a]	1[a]	1[a], 1	–	–	2[a]	–	–	–	–	–	–

[a] no occurence of recurrence

rate, in agreement with our results, is above 80% [3, 4, 6] and although no comparative study has yet been performed, historical controls at least indicate a striking advantage of intra-arterial over conventional treatment. It should be kept in mind, however, that there are contraindications for regional chemotherapy; in order to achieve an optimal clinical result, prerequisites like good vascularization and sufficient chemosensitivity must be met. Lesions in previously irradiated areas are unlikely to show good responses [5], though there are a few exceptions, one of which is published herein.

Patients who have already had chemotherapy also tend to be more chemoresistant than nonpretreated patients. This is often the case even with high-dose regional perfusion – although quite often chemoresistance can be overcome just by increasing the total dose [1]. Our group of patients with prior irradiation and chemotherapy had a 15% CR rate from regional chemotherapy, versus 42% in the nonpretreated group.

Despite the existence of several unanswered questions concerning the optimal drug combinations, infusion durations, and resulting tissue levels, regional chemotherapy via the subclavian artery is promising with regard to long-term remission and quality of life.

References

1. Aigner KR, Müller H, de Toma G (1988) Mitoxantrone in regional chemotherapy. In: Aigner KR, Patt YZ, Link KH, Kreidler J (eds) Regional Cancer Treatment. Karger, Basel, pp 49–57
2. Dedrick RL (1988) Arterial drug infusion: pharmacokinetic problems and pitfalls. JNCI 80: 84–89
3. Koyama H, Nishizawa Y, Wada T, Kabuto T, Shiba E, Iwanaga T, Terasawa T, Wada A (1985) Intra-arterial infusion chemotherapy as an induction therapy in multidisciplinary treatment for locally advanced breast cancer. A long-term follow-up study. Cancer 56: 725–729
4. Stephens FO (1983) Clinical experience in the use of intra-arterial infusion chemotherapy in the treatment of cancers in the head and neck, the extremities, the breast and the stomach. Recent Results Cancer Res 86: 122–127
5. Stephens FO (1988) Why use regional chemotherapy? Principles and pharmacokinetics. Reg Cancer Treat 1: 1–7
6. Stephens FO, Crea P, Harker GJS, Roberts BA, Hambly CK (1980b) Intra-arterial chemotherapy as basal treatment in advanced and fungating primary breast cancer. Lancet II: 435–438

Received October 5, 1988