Mitomycin C in Cancer Chemotherapy Today

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Regional chemotherapy for locally recurrent breast cancer—a phase II study with mitomycin C, fluorouracil/folinic acid

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Introduction

Only a few therapeutic alternatives can be considered for locally recurrent breast cancer at the chest wall. Previously, irradiation had been the method of choice, however relapse is often located in or around previously irradiated fields. Transposition of muscular cutaneous flaps is usually followed by recurrence in surrounding tissues. Because of insufficient local drug exposure, systemic chemotherapy has not so far produced convincing results in bulky tumors at the thoracic wall. In an attempt to increase local drug exposure, catheter techniques for selective regional drug application have been developed.

Methods

Catheterization techniques

A new access for permanent subclavian artery cannulation, including 3 variations, has been developed [1], and new experiences with this technique have been continuously applied for its improvement. The recent standard consists of a Jet Port Allround (PfM, Cologne) implantable port catheter, which is inserted with or without a retention rim at the tip, depending on the technique and on the site of vascular access. We generally aim at infusing the whole subclavian artery with all its side branches in order to achieve homogeneous distribution of the cytotoxic drugs over the whole chest wall, shoulder, and neck.

Catheterization via the axillary artery was most often used at the beginning of this study and was usually performed at the end of an axillary dissection for staging or removal of lymph node metastases. The artery is exposed amid

the nerve plexus and the free rimless tip of a Jet Port Allround catheter is then inserted by a thread and loosely fixed with a 5.0 prolene purse-string suture. Under Y-ray control with contrast medium, the tip of the catheter is then advanced to its final position. On the left side the technique is straightforward, since the tip can be positioned directly behind the origin of the subclavian artery from the aortic arch (Fig 1) and the port placed in an infraclavicular subcutaneous pouch. Care must be taken not to infuse the aortic arch. On the right side, as well as axillary access, the technique of choice is end-to-side placement of the tip of the catheter immediately behind the origin of the subclavian artery from the brachiocephalic trunk. Vascular access is achieved through a medial supraclavicular incision from the right edge of the jugulum, parallel to the clavicle.

First the internal jugular vein and common carotid artery are exposed. The subclavian artery is then found laterally behind the common carotid artery in a deeper layer. It is secured with a tape and gently pulled forward. Exposure is easier on the right side than on the left. The catheter used in this site is implanted in end-to-side technique through a stitch incision. The retention rim, positioned outside the vessel, serves to fix the tip by means of a prolene purse string (Fig 2).

In most cases the correct position of the catheter can easily be checked by bolus infusion of blue dye (indigo carmine) 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 3). Catheters must be flushed with heparinized saline immediately after therapy. Care must be taken to withdraw the needle with the syringe under pressure, because blood might enter and clot the catheter. For prophylaxis of arterial thrombosis one tablet of Aspirin Junior (100 mg) is administered daily. In the case of medial supraclavicular access (end-to-side) prophylaxis has been stopped after 2 months with no thrombotic complications to date.

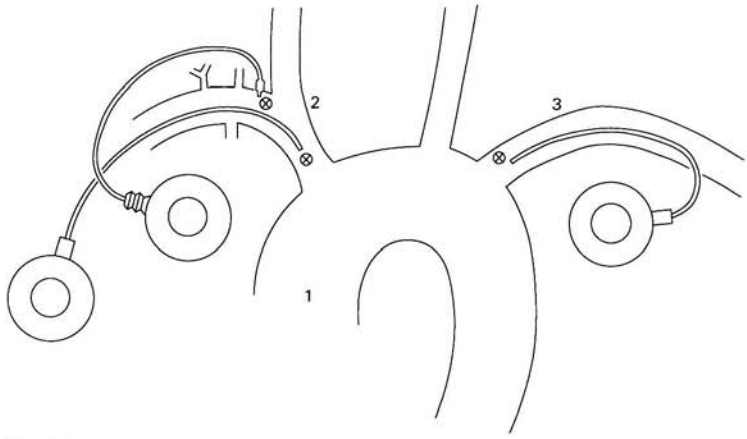


Fig 1 Positioning of subclavian artery catheters: 1, aorta; 2, brachiocephalic trunk; 3, subclavian artery.

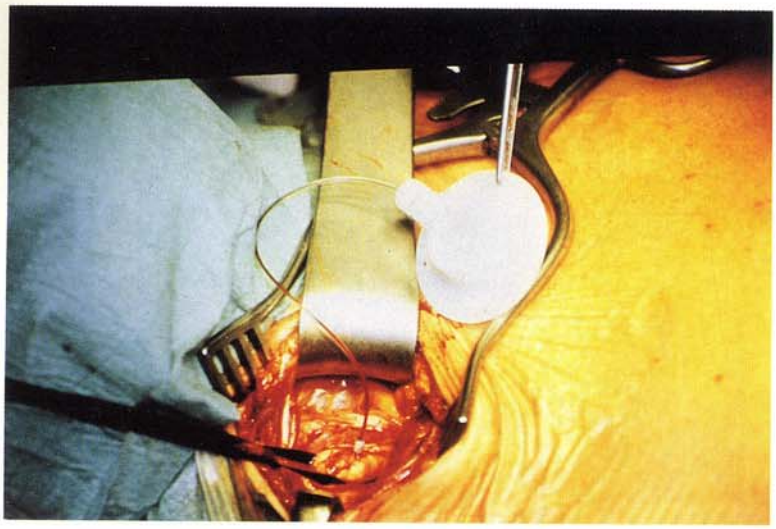


Fig 2 End-to-end implantation of Jet Port Allround catheter with rim tip.

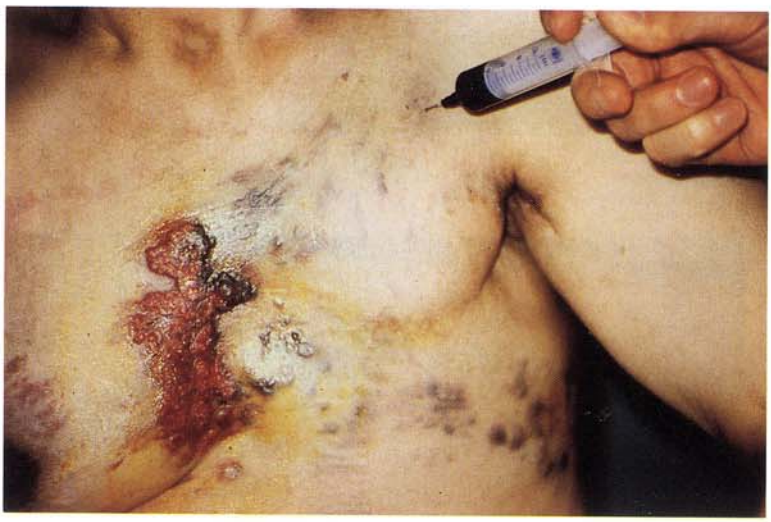
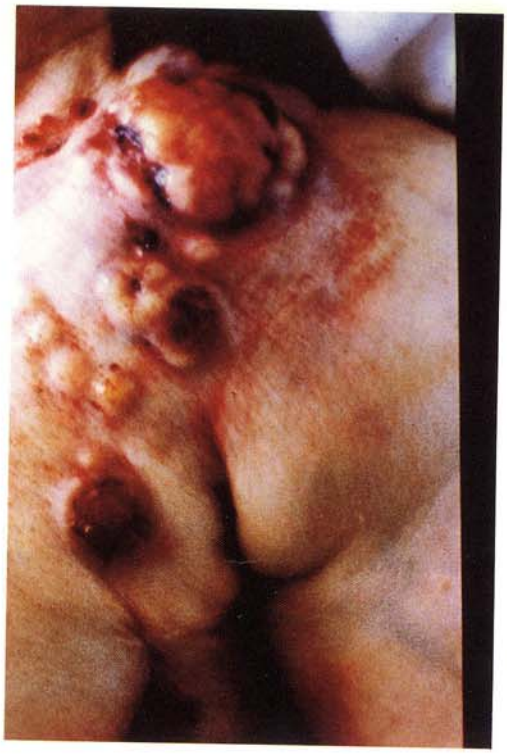


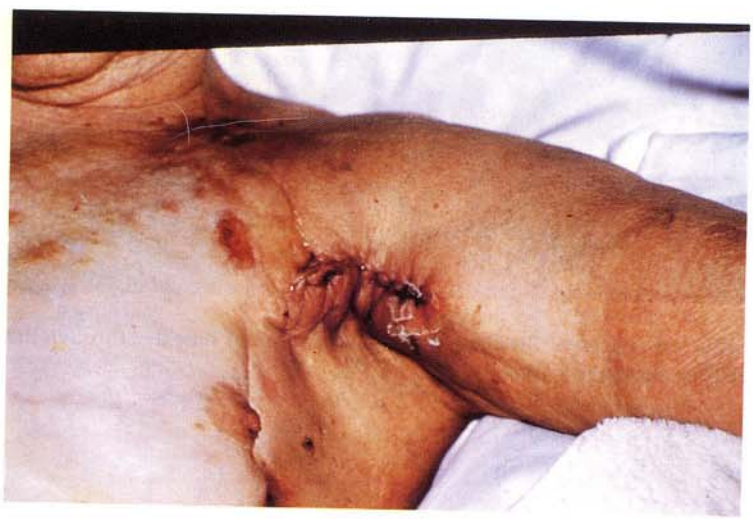
Fig 3 Blue coloration of the chest wall after injection of blue dye through the subclavian Jet Port Allround catheter.

Patients

Ninety-four patients with chest wall recurrences from breast cancer were entered into the study. The extent of the lesions ranged from small and widespread metastases to bulky disease with large tumor volumes infiltrating the muscular layers. Twenty-one patients had severe lymphedema and intractable pain and received their first cycle via angiographically placed catheters.

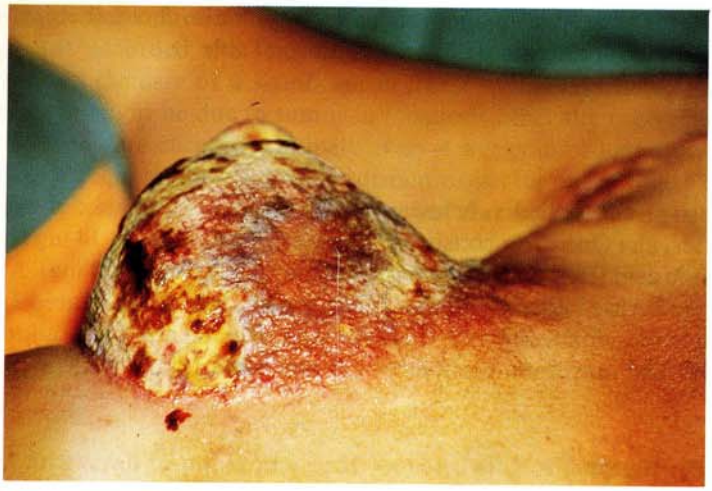


(a)

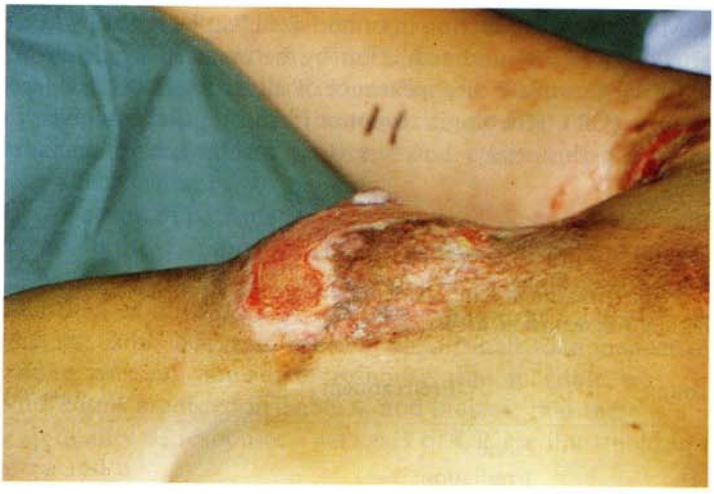


(b)

Fig 4 Bulky chest metastases from breast cancer before (a) and after (b) regional chemotherapy.



(a)



(b)

Fig 5 Fungating breast cancer before (a) and after (b) 2 cycles of regional chemotherapy.

Ninety-two patients had recurrent breast cancer. The remaining 2 patients had fungating breast cancer, one with multiple bulky metastases throughout the thoracic wall, so that there was little difference in size between the primary lesion and metastases (Figs 4a and b, 5a and b).

Patients were divided into 4 groups according to prior therapy, since prior irradiation can impair vascularization in the tumor area and thus reduce the

response to arterial infusion, and prior systemic chemotherapy may be responsible for induction of drug resistance (Table 1).

Chemotherapy

The most often applied subclavian artery infusion comprised 4 cycles at 4-week intervals. One cycle consisted of mitomycin C (MMC; 14 mg total dose) and folinic acid (Rescuvolin; 50 mg)/fluorouracil (5-FU; 1000 mg). MMC and 5-FU were infused over 60 min and folinic acid over 5 min (Table 2). In case of recurrence, doxorubicin 30 mg, infused over 60 min, was added to the schedule. The maximum number of courses given to any patient was 9.

Response criteria

The macroscopic effect was considered the main response criterion. Response was estimated almost exclusively according to clinical features and tumor markers. Macroscopic reduction in tumor size by at least 50% was considered a partial response (PR) and reduction by between 30% and 50% a minor response (MR). Complete disappearance of all lesions was considered a complete response (CR). Histologic response from biopsies was given increasing attention during this study, however these results are not included in this

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

Group	Pretreatment	No. of patients (n=94)
I	None	21
II	Irradiation	17
III	Chemotherapy	20
IV	Irradiation + chemotherapy	36

Table 2 Schedule for subclavian artery infusion chemotherapy for recurrent breast cancer. Reproduced, with permission, from Aigner KR [1].

Day	Drug	Total dose (mg)
1	MMC	14
2	Folinic acid/5-FU	50/1000
3	Folinic acid/5-FU	50/1000
1	Folinic acid/5-FU	50/1000

report. In addition, tumor markers were measured (CEA; CA 15-3); however they were not accorded the same importance as the macroscopic aspect, because even in the case of a significant decrease in markers, any remaining slight elevation might be due to tumor in locations other than the chest wall. Tumor markers were checked routinely every 4 weeks in order to detect any sudden changes that might originate in distant organ lesions. Clinical control studies were carried out after 4 initial courses of therapy and repeated every 3 months.

Results

Response

There was an overall response rate of 92%, consisting of 30% CR, 45% PR, and 17% MR. No reponse (NR) was recorded in 8% (Table 3). Response rates were higher among patients who had received no previous therapy (47.6% CR, 33.3% PR) compared with the group with prior irradiation and chemotherapy (13.9% CR, 52.8% PR).

The group with prior radiotherapy had a lower number of CRs (30%) compared with the group that had prior chemotherapy. The overall response rate, however, was somewhat higher in the preradiated group (85% vs 65%) than in the prior chemotherapy group, possibly due to chemotherapy-induced drug resistance in a major number of patients.

Sixty-seven percent of patients with severe lymphedema showed remissions, with a decrease in the circumference of the arm and substantial improvement or resolution of pain. All responders showed a measurable response within 4–10 days after the end of the first course. No response occurred after repeated courses with the same drug combination when it had been ineffective at the start. If there was no immediate response, the schedule was changed. Response durations are listed in Table 4, and indicate that there is a ranking according to quality of response. Two cases of CR are illustrated in Figs 4a and b and 5a and b.

Table 3 Reponse rates after subclavian artery infusion chemotherapy according to treatment (overall response 92%).

Pretreatment	CR (%)	PR (%)	MR (%)	NR (%)
None (n=21)	10 (47.6)	7 (33.3)	2 (9.5)	2 (9.5)
Chemotherapy (n=17)	7 (41.2)	5 (29.4)	3 (17.6)	2 (11.8)
Radiotherapy (n=20)	6 (30.0)	11 (55.0)	1 (5.0)	2 (10.0)
Radio- and chemotherapy (n=36)	5 (13.9)	19 (52.8)	10 (27.8)	2 (5.6)
Total (n=94)	28 (30.0)	42 (45.0)	16 (17.0)	8 (8.0)

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

Response	Total no. of patients (n=86)	Duration of remission (mo)
CR	28	11.6
PR	42	7.5
MR	16	4.4

Side effects and complications

The side effects were usually only moderate and had no effect on the patients' 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" [1–3] due to lack of turbulence in the subclavian bloodstream, resulting in spot-like "skin burn," and eventually tissue damage or even transient neurological or central nervous disturbances. Soft tissue damage at the shoulder or chest wall occurred in 4 patients who had undergone catheter implantation from the axillary access. Thrombosis of the subclavian artery occurred in 4 patients who also had axillary catheters, where aspirin prophylaxis was either not administered or stopped by the patient. Obviously there was sufficient time for development of collaterals, since the patients showed no clinical deficiencies. Local wound infections were observed in 3 cases.

Discussion

Intraarterial chemotherapy for advanced and fungating breast cancer has been described by some other groups in the past [1,4–8]. Cannulation of the subclavian or mammary artery has usually been achieved by angiographic placement of catheters or by means of surgically placed catheters that exited percutaneously. We have tried several techniques to implant permanent devices consisting of thin catheters of adjustable length connected to ports. Those systems were used for local recurrences, as well as for primary breast cancer [9].

At the thoracic wall, regional chemotherapy has the advantage over conventional therapies of a low complication rate, almost no local side effects, no systemic toxicity, and therefore good quality of life during therapy. The response rate, in agreement with our results, ranges between 80–90% [1,4,5,10,11], and although no comparative study has yet been performed historical controls at least indicate a striking advantage of intraarterial over conventional treatment. It must be pointed out that the vast majority of patients in our series had mostly bulky, widespread lesions encompassing

supraclavicular nodes and extended areas of the chest wall, and were not, therefore, candidates for surgery. The area of cytostatic drug distribution covered by subclavian artery vascular branches as a standard is by far larger than radiation fields usually are. The potential of administration of tumoricidal drug concentrations throughout the field of arterial infusion encompassing the whole upper quadrant and not carrying the risk of tissue or skin damage is considered to be a basic advantage. Local response rate and tumor control are higher than those reported in radiation studies [12,13]. 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 [3], due to impaired microvascularity, although in our study there is evidence that in patients in whom radiotherapy has preceded arterial infusion only by a few weeks or months, lasting hyperemia of radiated tissue may enhance the efficacy of regional chemotherapy. This might be a rationale for future protocols, combining low-dose radiation with arterial chemotherapy.

Patients who have previously had chemotherapy also tend to be more chemoresistant than nonpretreated patients. However, chemoresistance can often be overcome by increasing the total dose or—as in the isolation perfusion setting—the local concentration. Our group of patients with prior irradiation and chemotherapy had a 14% CR rate with regional chemotherapy, vs 48% in the nonpretreated group.

Despite several open questions concerning the optimal drug combination and local concentrations to be aimed at, regional chemotherapy via the subclavian artery is promising with regard to long-term remission and quality of life.

Acknowledgment

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