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Subclavian artery infusion as induction and adjuvant chemotherapy for breast conserving treatment of primary breast cancer

Research Article

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Summary

In recent years the management of breast cancer experienced a tendency towards breast conserving surgery combined with chemotherapy and irradiation. Surgery combined with chemotherapy for downsizing was applied in order to achieve resectability in large tumors or to keep the surgical intervention minimal. However, achievement of impressive response in terms of downstaging is a longlasting procedure, accompanied by prolonged toxic chemotherapy. In an attempt to achieve increased local drug exposure intraarterial infusion chemotherapy of the internal mammary and the subclavian artery was performed in 53 patients with primary breast cancer. The therapy consisted of six cycles of the three drug combination Mitomycin, Adriamycin and Cis-Platin. 34/53 patients had undergone local tumor excision prior to i. a. chemotherapy (IAC), 19/53 patients received induction (neoadjuvant) IAC and restaging with lumpectomy after three treatment cycles. Complete response was noted in 26 % and overall response was 74 %. A significant shift from T3/T4 stages towards T1/T2 was observed within three treatment cycles. Quality of life was generally good and most patients were able to work between the treatment cycles. Main side-effect was drugstreaming causing skin burns, which initially occurred in about 30 % and in recent years in 4 %. Local recurrence rate was 17 % and median survival was not yet reached within the follow up time of 16 years.

I. Introduction

The treatment strategy of breast cancer has changed remarkably during the past 3 decades. Radical surgery is no longer the treatment of choice. Breast cancer is considered a systemic disease already in early stages and therefore mutilating surgery has been abandoned to a great extent. Breast conserving surgery is aimed at whenever justifiable in most latest treatment protocols. Radical axillary dissection has been replaced by removal of the sentinel lymphnode in the first attempt. Radiotherapy maintained its position in combination therapies for destruction of potential axillary lymphnode metastases or for prevention of local recurrences. More importance is given to multidisciplinary management of disease (Carlson et al, 1999). If systemic chemotherapy would be sufficiently effective in the entire organism, local relapse or distant metastases should not occur - the dose-response relationship is steep" Emil Frei (Frei et al, 1980). If high-dose chemotherapy could generate sufficient efficacy (Görich et al, 1995; Merajver et al, 1997; Murakami et al, 2001) in the entire organism, resistant cell clones would no longer be resistant and could not survive. Regional chemotherapy, because of precalculated local drug concentrations, in many cases can generate the required drug exposure at the target site (Aigner, 1994; Sainsbury et al, 1990; Stephens, 1988; Stephens et al, 1980a,b; Wang, 1990).

II. Material and Methods

This study was performed in a series of 53 patients who refused mastectomy. In 19/53 patients, after three cycles of regional induction (neoadjuvant) chemotherapy a local excision of the lesion or the area of the prior lesion, respectively, was performed for pathological evaluation. 34/53 patients had had local tumor excision prior to regional chemotherapy. None of these patients had undersigned informed consent of mastectomy.

III. Treatment

All patients initially underwent catheter placement in Seldinger's technique and an arteriogram of the subclavian artery with its branches and the internal mammary artery was obtained. For contrast imaging of the vascular branches of the subclavian artery (Doughty et al, 1996), and as well to avoid infusion of the arm, a brachial pneumatic sphygmomanometer was inflated at least to 30 mm/Hg above the systolic pressure during the intraarterial infusion. In order to trace the target of intraarterial infusion and correct positioning of the catheter, indigocarmin blue was injected prior to each therapy. A total of six cycles of subclavian artery infusion (SAI) in four weeks intervals was performed with a three drug combination of mitomycin, adriamycin and cis-platin (**Table 1**). The average dose for one cycle was 10 mg MMC, two times 15 mg ADM and two times 30 mg CDDP.

During the first three cycles until local resection of the residual tumor, the first two days selective infusion of the internal mammary artery was performed with 10 mg each of Mitomycin and Adriamycin. Then the cycle was completed with subclavian artery infusion of Adriamycin and Cis-Platin according to the protocol.

In case the patient continued to be reluctant to any surgical intervention, angiographic therapy was continued throughout the six cycles. In case the patient agreed with surgical placement of a Jet Port Allround subclavian artery catheter (PfM Cologne), further therapies were performed through this catheter (**Figure 1**).

IV. Results

Local response in terms of tumor downsizing was the leading parameter. In 34 patients the primary tumor (stages T1-3) had been resected prior to adjuvant arterial infusion. In 19 patients, who underwent regional induction (neoadjuvant) chemotherapy, most evidently there was a remarkable shift from larger tumorsizes (T3, T4) down to lower sizes (T1, T2). In 26 % a complete remission was noted histologically (**Figures 2, 3**) 9 patients (48 %) had a partial remission, whilst 32 % of pretherapeutic T4 tumors were reduced to a histologically confirmed 11% T4 after

Table 1. Protocol of Subclavian Artery Infusion for Breast Cancer. Six cycles in four weeks intervals

Day	Drug	Dosage	Infusion Time
1	Mitomycin C	0,17 mg/kg	15 min
2	Adriamycin	0,25 mg/kg	15 min
3	Adriamycin	0,25 mg/kg	15 min
4	Cisplatin	0,50 mg/kg	15 min
5	Cisplatin	0,50 mg/kg	15 min

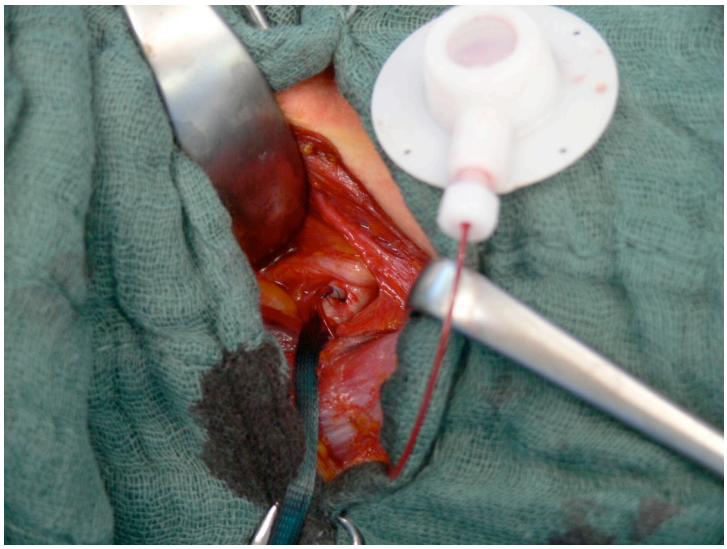

Figure 1. End-to-side implantation of subclavian artery Jet Port catheter

arterial chemotherapy. Vice versa, after arterial infusion of all patients the number of T1 sized tumors had increased from initially 10,5 % to 32 % after intraarterial chemotherapy (**Table 2**). Local recurrence rate after 16 years was 17 %. Kaplan Meier survival estimate is shown in **Figure 4**. After a 16 years follow-up the median survival time has not yet been reached. 9/53 patients (17 %) had a local relapse and 7 patients died from relapse and/or distant metastases.

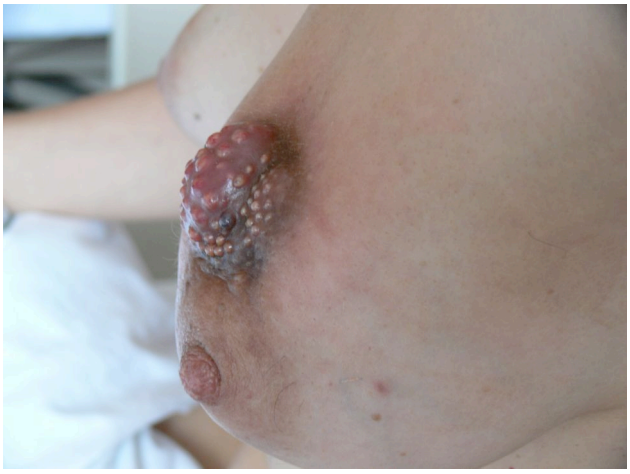

Figure 2. T4 primary breast cancer before therapy

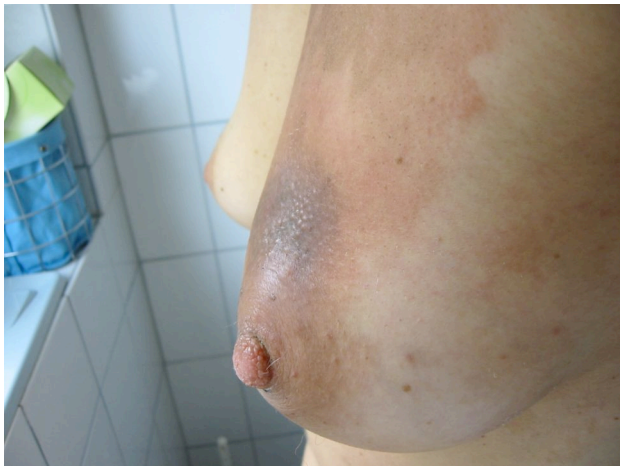

Figure 3. Complete remission after three cycles of intraarterial chemotherapy.

Table 2. Downsizing of primary tumors after 3 cycles of subclavian artery infusion (SAI).

TNM-Stage			
before SAI (n = 19)		**after SAI (n = 19)**	
		CR	n = 5 (26 %)
cT1	n = 2 (10,5 %)	pT1	n = 6 (32 %)
cT2	n = 9 (47 %)	pT2	n = 3 (15,75 %)
cT3	n = 2 (10,5 %)	pT3	n = 1 (5,25 %)
cT4	n = 6 (32 %)	pT4	n = 2 (10,5 %)
unknown		n = 2 (10,5 %)	

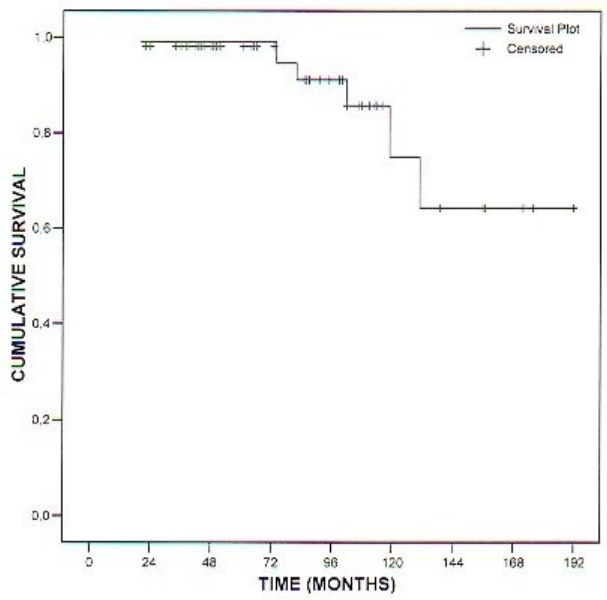

Figure 4. Kaplan Meier Survival estimate curve after SAI for primary breast cancer

Side-effects in general were moderate. There was no substantial haematologic toxicity that required antibiotic prophylaxis or substitution of blood components. Tiredness or fatigue have never been observed and patients usually were able to go to work between the treatment cycles. Hairloss mostly was moderate and normally did not occur. Only two patients had visible hairloss (4 %), one of them alopecia. The only real complication, causing problems, was drugstreaming, which, in the beginning had happened in every third case, but could be reduced later on to 4 % after applying the total amount of drug through a constant flow pump within 15 minutes.

V. Discussion

Breast cancer is considered a potentially systemic disease and therefore regional chemotherapy has been ranked as non adequate, treating only part of the area to be treated. The problem arising, however is, that systemic chemotherapy, in case of a bulky primary tumor, can hardly generate drug exposures, required for definite tumor eradication. And if so, dose- intense chemotherapy has to be intensified in such a way that toxicity becomes intolerable.

Regional chemotherapy, however, in terms of intraarterial infusion is not an isolated procedure, confined exclusively to one well defined segment of the body-like surgery or irradiation. Intraarterial infusion is a systemic therapy given with its first pass through the area to be treated firsthand, the target, which is the primary tumor in the breast and all its lymphatic drainages. The first pass through the arterial supply causes a concentration-dependent higher tissue uptake of cytotoxics in the area to be treated, but also a systemic drug exposure from the cytotoxics exiting the tumor area through the venous drainage.

The relatively small doses applied intraarterially are highly effective due to the drug concentrations achieved in arteries with comparatively moderate blood-flow, like the internal mammary artery.

It has been shown in a previous study (Aigner, 1994), that in locoregional therapy of breast cancer there is a steep dose-response relationship (Fiorentini et al, 2003), dependent on the applied technique. Therefore in the neoadjuvant cases, it was important to combine subclavian artery infusion with infusion of the internal mammary artery, the diameter of which is much smaller than the diameter of the subclavian artery and thus many generate a much higher and efficient drug concentration at the tumor site.

As a consequence, intraarterial application of drugs is more effective in terms of local control, when compared to systemic chemotherapy, where the same, or even higher doses are given intravenously (Stephens et al, 1980).

Regarding the response rates in the study presented herein, it is obvious that within only three cycles of regional chemotherapy a substantial response could be achieved, translating into a 26% complete remission and 74 % overall remission rate and a significant shift from large to small tumor diameters. Moreover, the recurrence rate of 17% over 16 years is remarkably low, taking into account that also T3/4 stages have been included in the study, and that all patients have been treated with local excision only, but without mastectomy. The survival estimate with seven deaths out of 53 treated patients throughout sixteen years suggests that the rate of distant metastases after i. a. infusion is not higher than has to be expected after systemic chemotherapy. This leaves one question open: Is systemic exposure from i. a. infusion as efficient as systemic exposures from systemic chemotherapy, or are both systemic exposures inefficient?

Regional chemotherapy for breast cancer is not at all a new method but all the same it never has had its breakthrough (Eedwinek et al, 1981; Carter et al, 1988; Noghuchi et al, 1988; Stephens, 1989, 1990; Wang et al, 1990; Dycker de et al, 1991; Görich et al, 1993, 1995; Takatsuka, 1994; Chrysos et al, 2001; Fiorentini et al, 2003).

Data from various published studies report approximately the same response rates as have been noted in our studies (Koyama et al, 1975; Koyama et al, 1985; Iwasa et al, 1988; Aigner et al, 1991, 1988; Dycker de et al, 1991; Nitz et al, 1993; Koyama, 1994; Morandi et al, 1996; Cakmakli et al, 1997; Mohrmann et al, 1999, 2000). At good quality of life they vary around 70%, a number that hardly can be achieved with other therapies without causing severe side-effects. This should be an argument to include the method into guidelines. The pioneers of intraarterial chemotherapy, Biermann and Klopp, after observing the local effect, called intraarterial chemotherapy, a “chemical irradiation” (Biermann and Klopp, 1951). Indeed it is as effective, and it does not cause tissue fibrosis.

But most evidently irradiation is easier to handle, and there are not sufficient clinical studies on intraarterial infusion for breast cancer, enough to justify inclusion of the method into treatment guidelines.

One of the main reasons might be the adverse effect encountered in most studies, which was drugstreaming and skin burns after internal mammary artery infusion (Ashaishi, 1994; Doughty et al, 1995; McCarter et al, 1995, 1998), we were confronted with the same complications and finally found out, that although a relatively small total dose was infused into the internal mammary artery, the local concentration that was generated was by far above the tissue tolerance. This complication can only be avoided by dilution of the total amount of drug to be applied in a bit larger volume, in combination with corticosteroids given the same route with a constant flow pump (Fiorentini et al, 2003) and not in a small volume through a hand syringe.

In conclusion, intraarterial infusion therapy for primary breast cancer can be an important tool, once the technique of application is standardized, allowing excellent results within a short time in favour of breast conservation and non-disturbed quality of life.

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