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# Regional chemotherapy – Editorial review article

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## Introduction

Regional chemotherapy has attained prominence over recent years for the treatment of primary and metastasised tumours, especially those with hepatic involvement. It provides an alternative to systemic chemotherapy, which has been shown to have limited benefits with only a small proportion of patients responding to therapy.

Intra-arterially administered regional chemotherapy is based upon a sound pharmacokinetic rationale, that the steep drug concentration gradient created between the arterial tree and the tumour tissue will result in an increased anti-tumour response [62]. In comparison, systemic (intravenous) chemotherapy delivers only a fraction of the administered dose to the tumour-bearing organ. Therefore, regional administration results in an increased local drug concentration, which, at least during first pass, exposes tumour cells to higher drug levels. This is beneficial for most chemotherapeutic drugs, although not necessarily for those with exceptionally high target clearance (e.g. idoxuridine for liver tumours). An additional benefit of regional chemotherapy exists with reference to its application in the treatment of liver and pancreatic cancer. During regional hepatic arterial administration, the metabolism and extraction of cytotoxic drugs by the liver may allow a high percentage of the cytotoxic to be eliminated, resulting in lower systemic concentrations. Consequently, a potential for a decreased systemic toxicity exists, although the degree varies with the target clearance. Drugs such as nitroureas and doxifluridine have been administered intrahepatically in much higher doses than can be tolerated when given systemically.

Regional chemotherapy is confined to use in a single body region, and limited by the blood supply to, and normal tissue tolerance of, the infused region. To date, the liver has been the organ to which regional chemotherapy has been most extensively administered, however, the breast and intra-abdominal cavity, in particular the pancreas, have also been described as potential organs for the application of regional chemotherapy.

The liver, as a consequence of its dual blood supply, is particularly suited for the application of regional chemotherapy. In humans, the blood supply to liver tumours is primarily obtained from the hepatic artery, whilst the normal liver parenchyma is supplied by the portal circulation. Cannulation of the hepatic artery, therefore, allows cytotoxic drugs to be administered specifically to the tumour area, while normal liver parenchyma is oxygenated and supported nutritionally by the portal circulation [11].

The application of regional chemotherapy in the treatment of breast tumours is relatively recent and has yet to be fully evaluated. However, studies have shown that effective regional chemotherapy can be administered if the internal mammary artery or the subclavian artery are used for cannulation. The internal mammary artery supplies the blood to the mammary gland and the parasternal lymph nodes, whereas the subclavian artery supplies the blood to the lymph nodes in the axilla and the supraclavicular fossa, and subselectively to the mammary glands [8]. Since a high percentage of breast tumours have the potential to metastasise to the lymph nodes, it is important that intra-arterial chemotherapy is delivered to a wide, yet specific, area of tumour involvement.

The use of regional chemotherapy in the treatment of pancreatic cancer is particularly complicated due to anatomical limitations. Unlike the liver, the arterial network and lymphatic drainage of the pancreas is diverse and highly variable. Tumour spread to the lymphatic system is common, and is often diffuse and precocious. It is, therefore, essential that the intra-arterial administration of cytotoxic drugs reaches not only the actual tumour site, but also the lymph nodes. Studies have shown that a right-gastro-epiploic catheter implantation in the direction of the pancreas allows the cytotoxic to circulate to the head, the neck, and the whole body of the pancreas. Furthermore, the drug reaches the main lymph nodes of the pancreas [19]. Infusions *via* the celiac axis and supe-

rior mesenteric artery have also proven to be effective [3, 5, 24]. These routes of administration have the potential for a decreased systemic toxicity as a result of metabolism of the cytotoxic by the liver.

The advantage of regional drug exposure is related to the rate of blood flow through the target organ, and is affected by the drug extraction ratio of the target organ, which reduces systemic drug toxicity and associated side effects. In attempting to further exploit the advantages of regional administration of anti-tumour drugs, attention has focused on various methods by which the rate of blood flow through the target organ can be decreased and systemic toxicity reduced.

This review details the current status of regional cancer treatment and the clinical benefits offered by some of the most recent regional, therapeutic approaches used for the treatment of not only liver cancer, but also breast and intra-abdominal carcinomas. The potential application and benefits of such treatment options are discussed.

## Factors affecting regional chemotherapy

### *Reduction of blood flow*

The rationale for reducing or halting blood flow is to increase the *in situ* time and tumour exposure of any co-administered cytotoxic drug, thus improving the efficacy of the cytotoxic. Reduction of the blood supply to target organs has been investigated, and various devices and arterial blocking agents identified [46, 52, 56, 71]. These may be categorised into three main groups: mechanical hepatic de-arterialisation of a permanent (hepatic artery ligation) or intermittent (tourniquets or balloon catheters) nature; embolisation provided by polyvinyl alcohol (Ivalon®), albumin, collagen and gelatin sponge particles (Gelfoam®) which promote vascular blockade for a period of several days to 6 months; and occlusion of a more transient nature (*in vitro* $t_{1/2}$ = 25 minutes at 37°C) elicited by degradable starch microspheres (DSM, Spherex®). Few of the available embolic agents have been systematically evaluated, however, in contrast, DSM has been comprehensively documented.

DSM are produced from hydrolysed potato starch, and are cross-linked by an emulsion polymerisation process using epichlorohydrin. Although the precise mechanism of action of DSM-induced occlusion is unclear, sufficient data are available to postulate their mode of action. As a consequence of their size (45 ± 7 μm), DSM become lodged in the precapillary vessels of the target organ [39]. Temporary occlusion of approximately 80% of blood flow is induced for a period between 15 and 80 minutes [7, 17, 26, 36], after which the spheres collapse and disappear. The period of vascular occlusion varies between individuals and is dependent on the DSM dose, the size of the vasculature of the tumour, and the organ as a whole.

The size and degradable characteristics [39] of DSM provides many favourable properties, including tumour-selective targeting of co-administered drugs through preferential tumour occlusion [60], promotion of portal wash-out [47, 60] and the ability to elicit tumour blood flow redistribution while avoiding collateral circulation [14, 16]. The short occlusion and ischaemic time also prevents development of post-embolisation syndrome, an undesirable effect that is frequently encountered with the more permanent embolic agents. This makes it possible to perform DSM-induced chemo-occlusion as an out-patient therapy, which is an important benefit for both the patient and the hospital.

The properties of DSM, together with preclinical and clinical results, have been comprehensively reviewed in recent publications [9, 34, 65, 66, 67] and its application in the treatment of liver, breast and pancreatic cancer is discussed below, in the section on indications for regional cancer treatment.

### *Systemic toxicity 'rescue' therapy*

Regional chemotherapy has been successful in reducing undesirable systemic toxicity associated with intravenous cytotoxic drug administration. However, additional methods to reduce toxicity are required, especially in the light of new, high-dose chemotherapy regimens. One such technique, chemofiltration, combines intra-arterial infusion of chemotherapeutic drugs with filtration/haemodialysis. This allows the administration of increased local concentrations of the cytotoxic drug, while limiting systemic drug exposure and hence side-effects [2, 70]. Chemofiltration has been used, in general, in those patients who have previously failed to obtain any tumour response to regional disease with systemic chemotherapy[70].

Whilst the performance of the haemofiltration unit is not affected by the dose of chemotherapy administered, the ultrafiltrate concentration has been shown to be dependent on flow rate [25]; the extraction of cytotoxic being greater at faster flow rates. Up to 45% of the total cytotoxic dose may be cleared at 400 ml/min flow rate, at which flow the ultrafiltrate amount correlates to the total administrated dose. Doubling the flow rate to 800 ml/min increases the filtration rate significantly by a mean of 2.2. In order to increase the extraction of cytotoxic drugs and correct the acidosis induced by haemofiltration exchange, it is necessary to dialyse the blood coming from the haemofilter before it returns to the patient. This dialysis improves drug extraction by 5-8% of the total dose [25].

### *Combination therapy*

Regional administration of cytotoxic drugs may be combined with alternative therapeutic strategies in order to enhance treatment success rates in patients with liver, breast, and intra-abdominal carcinomas [11, 38, 64]. For example, multimodular therapies combining chemo-oc-

clusion, chemofiltration and systemic chemotherapy may provide local tumour control whilst reducing normal tissue exposure, systemic tumour spread and tumour progression, thereby limiting recurrence rates.

Induction chemotherapy

Induction chemotherapy describes the combination of regional chemotherapy followed by resection surgery. Its aim is to reduce the size of large tumours, creating a tumour necrotic area, in order to provide the potential of surgical resection of an otherwise unresectable tumour. The ability of regional chemotherapy to slow down or halt tumour development and, if administered with an occlusion agent, to elicit tumour necrosis, makes this an attractive option, and induction therapy has been assessed in a number of studies. For example, a hepatic cytoreduction protocol involving induction chemotherapy has been described by Sugarbaker & Steves [64].

Adjuvant therapy

Despite the use of regional therapies prior to surgical resection of a tumour, the rate of tumour recurrence in many patients will remain very high. Patient survival can only be improved substantially if tumour recurrence can be reduced or prevented. A recent study has suggested that regional chemotherapy administered with an occlusive agent would offer the best opportunity for reducing the incidence of tumour recurrence following surgical resection of hepatocellular carcinomas [69]. Since hepatocellular carcinoma is often multifocal, regional chemotherapy may well be beneficial in treating micrometastases that have escaped resection, thereby reducing the potential for intra-hepatic tumour recurrences. Additionally, the risk of metastases and tumour spread during surgical manipulations of primary breast or intra-abdominal cancers may also be reduced by the application of regional chemotherapy, thus reducing the incidence of recurrence of these tumours. The use of radiotherapy, following regional chemotherapy and surgical resection of the tumour, may also further aid the control of tumour spread.

Extra-target progression

Systemic spread of tumour cells is a frequent event in the progression of many cancers, therefore regional treatment regimens should perhaps be supported by complementary systemic chemotherapy. Systemic chemotherapy might thus be administered after regional chemotherapy and/or resection in an attempt to improve patient survival, and in addition when subclinical disease is suspected [33, 50, 58].

Immuno-occlusion

Since regional chemotherapy allows direct delivery of agents to the tumour site, it has been proposed that cellular regulators, in particular cytokines, could be co-administered with cytotoxic drugs and an embolic agent [57]. As cancer is a disorder of cellular regulation, it is thought that the administration of cytokines, which are powerful regulators of normal cell behaviour, would provide a potential for controlling the growth of malignant cells.

Sequence of modalities

The sequence of use of combination therapies must be caref ully evaluated if the efficacy of a particular therapy is not to be compromised. Recent studies have suggested that the efficacy of intra-arterial chemotherapy may be reduced, as a result of vascular damage, if it is administered following radiotherapy [6, 49, 62]. Furthermore, systemic chemotherapy may be compromised if the toxicity of regional chemotherapy is not confined to the region infused. This is particularly relevant in the treatment of breast cancer, where an intra-arterial dose of chemotherapy will not undergo extraction on first pass, as is the case following hepatic and pancreatic cytotoxic administration. The potential for high systemic toxicity and poor patient tolerance therefore exists.

## Indications for regional cancer treatment

The morbidity and mortality of patients with liver, breast, pancreatic and gastric tumours remain high, with response rates to treatment being poor. As a result, research into the treatment of these cancers is paramount and new approaches are continually being investigated. Regional chemotherapeutic strategies are one of the approaches currently being evaluated. Whilst data on the use of regional chemotherapy in liver cancer are available, its application in breast and intra-abdominal cancers is still relatively new.

### *Liver cancer*

Despite advances in diagnostic and therapeutic techniques, patients with liver malignancies (primary tumours or liver metastases) have a poor prognosis. Indeed, life-expectancy for these patients is only approximately 6 months [44] and, although there are anecdotal reports of long-term survival, virtually all patients with untreated liver malignancies die within 2 years of diagnosis.

Surgical resection is, at present, the only curative form of treatment, but is successful in only 10-20% of patients [44]. Furthermore, the overall value of surgery is limited, because only a small proportion of patients (5-30%) have tumours that are suitable for resection [72]. For example, the presence of multiple or inaccessible tumours, or the occurrence of extrahepatic metastases and affected lymph nodes, precludes this treatment option.

Systemic chemotherapy provides an alternative approach in treating liver cancer, however, few patients (approximately 20%), irrespective of whether the tumour is primary or metastatic, demonstrate a tumour response [21, 32, 34]. Indeed, median survival is only 5-7 months

after diagnosis [21, 34] and patients suffer the side effects associated with systemic cytotoxic drug administration. It is thus evident that, administered alone, systemic chemotherapy is ineffective and inappropriate for the treatment of liver tumours, especially as alternative treatment options are available.

Regional chemotherapy

Several studies have demonstrated that intra-hepatic arterial infusion of cytotoxic drugs provides a significantly higher tumour response than does systemic chemotherapy [12, 29, 35, 41, 54]. Indeed, in two studies survival was enhanced [12, 54]. Systemic toxicity is elicited by both systemic and regional treatments; regional chemotherapy provides different complications than conventional systemic chemotherapy. Furthermore, problems such as infection and drug leakage from catheters have been experienced during regional chemotherapy. These problems are more pronounced in patients receiving continuous infusion *via* a port infused by external pumps than in patients in whom a totally implantable pump is used [13]. Nevertheless, regional chemotherapy has obvious clinical advantages when compared with systemic chemotherapy in the treatment of liver cancer.

The efficacy of regional chemotherapy may be improved by the concomitant use of embolic and occlusive agents or chemofiltration. Metastatic liver tumours tend to be solid in nature and as a consequence are associated with high interstitial pressure, a predominant peripheral capillary location and increased capillary thickness. As a result of these factors the ability of a cytotoxic drug to permeate a tumour is reduced, the efflux of the drug from the tumour to extratumoural tissues is enhanced, and hence the efficacy of regionally administered cytotoxic drugs is reduced. The application of chemo-occlusion and/or high-dose regional chemotherapy has been proposed in an attempt to improve the efficacy of regional chemotherapy in solid tumours.

Chemo-occlusion

The use of chemoembolisation with Gelfoam®, Angiostat® and Ivalon® and the use of Lipiodol® (iodized oil contrast medium) have been shown to provide some therapeutic benefit in patients with liver cancer, however, in general, studies have comprised only a small patient sample and have been non-comparative [46, 52, 56, 71]. In contrast, DSM induced chemo-occlusion has been studied in several phase II trials (Table I) and in a comparative, randomised phase III clinical investigation [68], with encouraging results. When evaluating the results from the phase II studies it should be remembered that, in several of these, the development of DSM-induced occlusion was in its infancy and the therapy was administered sub-optimally. In the most recent study [15], both the complete response and the partial response rates were 22%.

In the phase III study reported by Taguchi et al. [68], the efficacy of intra-arterial chemotherapy plus DSM was compared with that of intra-arterial chemotherapy alone in 120 patients with unresectable hepatocellular carcinoma or metastatic liver cancer. In the hepatocellular carcinoma arm of the study, the tumour response rate (complete and partial responses) of patients receiving doxorubicin plus DSM was 36.4%, whereas the corresponding value for patients receiving doxorubicin alone was 9.5% ($P<0.01$). In metastatic liver cancer patients, the tumour response rate of those treated with mitomycin C plus DSM was 54.5%, compared to a response rate of 20.0% ($P<0.05$) in patients receiving mitomycin C without DSM. Although factors such as time to tumour progression and survival were not directly addressed by this phase III trial, the median survival time of DSM-treated patients was slightly longer than that for patients receiving cytotoxic alone. Clearly, this randomised study, the first utilising an embolic/occlusive agent, shows promising results in terms of tumour response rates. Further randomised trials, with much larger patient numbers, should be performed to confirm these results and potentially to detect statistically significant differences in patient survival.

High-dose regional chemotherapy and chemofiltration

The introduction of an increased dose of cytotoxic drug to the tumour area provides the potential for greater intracellular drug concentration, and hence increased tumour necrosis. However, increased circulating levels

**Table I:** Summary of results obtained in 18 phase II clinical studies: tumour response to co-injected DSM and a cytotoxic agent*

| Total number of patients evaluated for response | Responses | Number of patients (%) |
|---|---|---|
| 427 with primary or secondary liver cancer in 18 studies | CR | 20 ( 5%) |
| | PR | 125 (29%) |
| | MR or NC or SD | 58 (13%) |
| | PD or not stated | 224 (52%) |

Abbreviations:
CR = complete response; PR = partial response; MR = minimal response; NC = no change; PD = progressive disease; SD = stable disease

* Cytotoxic agents:
5-FU, BCNU, cisplatinum, doxorubicin, epirubicin, fotemustine, FUDR, Mitomycin C

of cytotoxic drug result in increased systemic drug exposure and toxicity, and hence increased side-effects. In order to limit systemic drug exposure, the technique of chemofiltration has been investigated. This combines intra-arterial infusion of high doses of chemotherapeutic drugs with filtration/haemodialysis.

To date, few studies have evaluated the efficacy of chemofiltration in high-dose locoregional chemotherapy for liver cancer. In a study reported by Fiorentini et al. [22], hepatic arterial infusion of high-dose chemotherapy with chemofiltration was compared with hepatic arterial infusion of prolonged low-dose chemotherapy in 42 patients with liver metastases from colorectal cancer. Twenty patients received an intra-arterial infusion of mitomycin C (30-50 mg/m$^2$) and epirubicin (60-90 mg/m$^2$) on the first and last day of therapy, the intervening 4 courses of chemotherapy comprised of a combination of mitomycin C (6 mg/m$^2$), epirubicin (29 mg/m$^2$) and fluorouracil (250 mg/m$^2$) infused every 2 weeks. Chemofiltration was performed in these patients by a double lumen filtration catheter placed in the inferior vena cava. Low-dose regional chemotherapy comprising mitomycin C (6 mg/m$^2$), epirubicin (20 mg/m$^2$) and fluorouracil (250 mg/m$^2$) was delivered to a further 22 patients. Results demonstrated a significant increase in response rates and in survival benefit associated with the high-dose regional chemotherapy and chemofiltration as compared to that seen with low-dose regional chemotherapy. Indeed, a response rate of 65% was achieved following regional chemotherapy and chemofiltration, with one and two year survival rates of 69% and 38%, respectively. In comparison, a response rate of only 33% was seen following low-dose intra-arterial infusion chemotherapy, with survival rates of 39% and 15% at one and two years, respectively [22]. However, over 50% of patients still experienced systemic toxicity, despite receiving chemofiltration.

In a smaller phase I study, comprising 16 patients with liver metastases from colorectal carcinomas, haemofiltration and/or haemodialysis of suprahepatic venous blood was performed during repeated intra-arterial infusion of mitomycin C (30 mg/m$^2$) by the use of a double lumen catheter (16F) introduced into the inferior vena cava. The mean reduction of mitomycin C bioavailability was 42.3% following haemofiltration, 54.4% following haemofiltration and haemodialysis, and 64.6% following two cycles of haemodialysis. Twenty-five per cent of patients had a complete response and 37.5% of patients had a partial response [27]. Similarly, a phase I study comprising 13 patients with metastatic liver cancer demonstrated a complete response of 15%, with a disease-free period of 25 months, and a partial response of 69% with a mean survival time of 16 months in patients following high-dose locoregional chemotherapy and chemofiltration [27, 28]. In a further study comprising 5 patients, intra-arterial infusions of doxifluoridine were administered over 90 minutes, the infused dose ranging between 1.5 g/m$^2$ and 6 g/m$^2$. Results demonstrated a reduction in toxicity with no neurological or haemopoietic toxicity, however, a partial response lasting 8 months was achieved in only one patient [23].

Lower nephrotoxic and gastro-intestinal side effects compared to systemic therapy have also been noted by Taton et al. [70] and, in addition, a less frequent incidence of anaemia and thrombocytopenia have been reported by Aigner & Gailhofer [2]. Furthermore, it has been shown that chemofiltration provides an enhanced quality of life to patients, as compared to those receiving chemotherapy alone, who experienced severe tiredness and symptoms that prompted longer hospitalisation [2].

Thus, preliminary results would tend to suggest that high-dose intra-arterial chemotherapy, when combined with chemofiltration, provides a reduced immediate systemic cytotoxicity and an effective therapeutic treatment in metastatic liver cancer. Indeed, a profound increase in patient survival rate was demonstrated in comparison to that achieved with prolonged low-dose intra-hepatic chemotherapy alone. However, only few studies, with small numbers of patients, have been undertaken utilising high-dose regional chemotherapy and chemofiltration. Larger, randomised clinical trials are therefore required to demonstrate more fully the efficacy of high-dose regional chemotherapy and chemofiltration in metastatic liver cancer.

Combination of regional chemotherapy with other therapeutic regimens

i) Induction chemotherapy (neoadjuvant)

As discussed above, the concept of induction therapy with regional, with the aim of retarding/halting tumour evolution or effecting tumour downstaging, is attractive because it could allow surgical resection of previously inoperable cancers. Preliminary studies in which chemoembolisation was used prior to surgery have shown promising results [37, 42, 45, 55, 73], with histological examination revealing high rates of tumour necrosis [37, 45, 55]. Even in cases where the tumour size is relatively large (5.6-12.0 cm), inductive chemoembolisation facilitates surgical resection, by promoting tumour regression [73].

Historically, Gelfoam® has been the most frequently used induction treatment. However, there is scope for investigation of the use of other embolising/occluding agents in this context. Certain complications associated with long-term vascular embolisation (vasculitis, hepatic artery thrombosis and tumour abscess) are highly undesirable if surgery is to be performed [10]. Chemo-occlusion as induction therapy may prove to be advantageous, as the temporary occlusive nature of DSM minimises vascular damage.

For hepatocellular carcinoma patients in whom surgical resection is contraindicated, the possibility of liver replacement therapy exists, with a good prognosis if extrahepatic metastases are absent. Due to its potential for eliciting tumour necrosis and decreasing recurrence rates, the use of induction chemoembolisation (or chemo-

occlusion) may be of use in liver replacement candidates awaiting a suitable donor.

ii) Adjuvant therapy

Prevention of tumour recurrence is of crucial importance after hepatic resection of hepatocellular carcinomas. However, recurrence rates are high, particularly in the cirrhotic liver. Adjuvant chemoembolisation (or chemo-occlusion) may be of use in the treatment of micrometastases that have escaped resection.

Önal et al. [48] studied the use of adjuvant intra-arterial chemotherapy in 9 patients following hepatic resection, obtaining a remission rate of 85.6%. This suggests that adjuvant therapy of this type may be useful in preventing recurrence in the liver. Recently, tumour response and survival were investigated in hepatocellular carcinoma patients with main portal vein tumour thrombus. It was found that hepatectomy and resection of the tumour thrombus, followed by postoperative transcatheter arterial embolisation (Lipiodol® mixed with a cytotoxic plus Gelfoam®) is perhaps superior to other treatment options for cases of this type [69]. It would seem that chemoembolisation and chemo-occlusion have considerable potential for adjuvant therapy to reduce intrahepatic tumour recurrence following surgical resection or transplantation.

iii) Systemic therapy

Regional chemotherapy only treats tumours locally, therefore systemic spread is possible and likely. Indeed, in a recent study, one of the most important prognostic factors for patients with colorectal liver metastasis receiving regional chemotherapy was the development of extrahepatic metastases [53]. Thus, combination of optimal systemic chemotherapy with regional chemotherapy may be effective in treating extrahepatic progression [33, 50, 58].

Additional studies are obviously required to further evaluate the effectiveness of combination therapies in the treatment of primary and metastatic liver cancer.

*Breast cancer*

Treatment in the form of surgical resection of the tumour, systemic chemotherapy, hormonotherapy and locoregional radiotherapy are currently the most commonly applied methods of treating breast cancer. However, the therapeutic efficacy of both systemic chemotherapy and radiotherapy treatment regimens has been questioned. Treatment of breast tumours by systemic chemotherapy results in poor patient prognosis, systemic toxicity and, with time, can lead to drug resistance. Indeed, such treatment of loco-recurrent breast tumours achieves only a poor complete remission rate, providing little or no therapeutic benefit, and cure remains elusive for many patients.

Radiotherapy, in comparison to systemic chemotherapy, appears to provide a higher rate of remission from breast cancer. The administration of radiotherapy following surgical resection of a breast tumour has been shown to reduce local regional tumour recurrences to 3-5% [38]. However, if local tumour recurrence does indeed occur, then the administration of further doses of radiotherapy results in an inadequate remission rate. Furthermore, at least 50% of patients receiving radiotherapy also require adjuvant systemic chemotherapy [43], albeit that the combined therapeutic value of systemic and radiotherapy has been shown to be relatively poor. Vascular damage [49], patient intolerance and poor cosmetic results [43] also result from radiotherapy.

The advent of regional chemotherapy, and its successful application in the treatment of liver carcinoma, has prompted many researchers to apply the principles of regional chemotherapy to the treatment of primary and locally recurrent breast cancer. Although the treatment of breast cancer by local regional chemotherapy is still in its infancy, preliminary studies have described the feasibility of such administration [6, 20, 38, 43, 49, 59, 61, 63]. Indeed, the poor treatment efficacy of radiotherapy and systemic chemotherapy in advanced breast cancer is emphasised when compared to the 50% complete response rate achieved with regional intra-arterial chemo-occlusion techniques [6].

A number of methods exist by which chemotherapeutic drugs can be regionally administered. Intra-arterial chemotherapy in breast cancer can be achieved *via* selective cannulation of the *arteria subclavia* [6, 38], and superselective cannulation of the *arteria mammaria interna* or the *arteria thoracica lateralis* [38, 43]. Chemotherapeutic agents have been administered through temporary radiologic catheters [38], surgically implanted catheters and implantable ports [6], by either infusion or by bolus injection. Particular benefits of various techniques have been observed. The application of a balloon catheter, which when inflated firmly holds the catheter tip in place, reduces the potential for cytotoxic drug infusion into the vertebral artery, thereby reducing the potential for neurological problems. The application of an upper arm tourniquet furtheron generates a much higher drug concentration at the target area. Moreover, following angiographic catheterisation, a port or pump can be implanted. This has the advantage of remaining in place indefinitely, without risk of thrombosis, delivering the necessary chemotherapy over a protracted time period. The placement of such a device removes the need for hospitalisation, allowing the patient to be treated on an out-patient basis.

In a study comprising of 144 patients with locally recurrent breast cancer, intra-arterial chemotherapy was delivered *via* an implantable port catheter (Jet Port Allround®) into the subclavian artery [6]. Patients received infusions of mitomycin C and 5-FU, with or without doxorubicin. Upper arm tourniquets and subclavian artery balloon catheters were applied in a number of patients. An overall tumour response rate of 89% was reported. In a similar phase II study of 46 patients with

locally recurrent breast cancer, consecutive infusions of mitoxantrone (14 mg/m$^2$) over 30 minutes, folinic acid (120 mg/m$^2$) over 30 minutes, and 5-fluorouracil (5-FU) (1.5 g/m$^2$) over 20 hours were administered into radiological catheters placed in the subclavian artery, the internal mammary artery or the lateral thoracic artery. An upper arm tourniquet was applied during the first 30 minutes of the arterial infusion and, depending on the radiotherapeutic pretreatment, all patients received additional local radiation. After 2 to 4 cycles of treatment an overall tumour response rate of 89% was reported, with 61% of patients in local tumour remission after a mean follow-up of 10 months [38].

Despite the advantages of regional intra-arterial chemotherapy, limitations to the technique do exist, and, as described previously, are allied to the rate of blood flow through the arterial circulation. The application of blood flow modulation with regional chemotherapy can overcome some of these difficulties. Regional intra-arterial chemotherapy has been used in conjunction with various forms of occlusion in some breast cancer patients, with promising results [6]. Interruption of the blood flow was achieved by upper arm tourniquet and subclavian artery balloon catheters. Preliminary results in 31 patients demonstrated a 50% complete remission rate following treatment. Unfortunately, no comparative studies utilising such techniques have, as yet, been undertaken in the treatment of breast cancer.

Regional chemotherapy has, in a few studies, been administered as an induction chemotherapy in the treatment of primary breast carcinomas with encouraging results [20, 43, 59]. In a study of 21 patients undergoing breast conserving treatment of the primary lesion, mitomycin C (10 mg) was injected prior to a 30 minute infusion of mitoxantrone (30 mg) into the internal mammary and lateral thoracic artery [20]. After 2 cycles of treatment, surgical resection of the tumour was performed. An overall response rate of 90% was obtained, with no locoregional recurrence after a mean follow-up of 30 months. In a similar study, comprising of 23 patients undergoing regional chemotherapy prior to subcutaneous mammorectomy and prosthetic replacement, mitoxantrone and melphalan combined were injected into the internal thoracic artery [43]. The aim was to deliver a target dose of above 16 mg/kg of breast weight. Systemic chemotherapy, comprising of epirubicin and cyclophosphamide, and hormonal therapy was also administered post surgery. A complete remission in 64% of patients was achieved, with 90% of patients disease free after a mean follow-up of 25 months. A similar response rate was seen when epirubinicin, mitomycin C and 5-FU were infused together into the subclavian artery [59].

Treatment order

Recent evidence has suggested that the efficacy of regional chemotherapy is compromised if administered following systemic chemotherapy and/or radiotherapy. As shown in Table II, regional chemotherapy following systemic chemotherapy plus radiotherapy, or following radiotherapy alone, provide only a 10% and 33% complete response rate, respectively, as compared to the 50% complete response rate noted when regional chemotherapy was applied with no pre-treatment [6]. Thus, it would seem that the timing of regional chemotherapy is important.

**Table II:** A comparison of tumour response rates in locally recurrent breast cancer patients receiving regional chemotherapy following various therapeutic pre-treatments (Aigner et al. 1993).

| Pre-treatment | CR (%) | PR (%) | MR (%) | NC (%) |
|---|---|---|---|---|
| None | 50 | 50 | – | – |
| Chemotherapy | 70 | 20 | – | – |
| Radiotherapy | 33 | 67 | – | – |
| Chemotherapy and Radiotherapy | 10 | 70 | – | 20 |

CR = complete response; PR = partial response; MR = minimal response; NC = no change

This phenomenon has been investigated by Pape et al. [49], who determined the influence of radiation induced vascular damage on the efficiency of intra-arterial chemotherapy by measuring the nutritive capillar density in local regional recurrences of breast cancer after irradiation. Results demonstrated vascular damage, a reduction in vascular density and consequently a reduction in blood supply to the irradiated region. Of those patients who received local regional chemotherapy with no pre-irradiation, 4.8% had a complete remission and 48% had a partial remission. In comparison, those patients who were irradiated prior to regional chemotherapy had no complete remission and only 11% had a partial remission. These results suggest that radiation-induced vascular damage significantly reduces response rates and compromises the efficacy of regional chemotherapy.

At present, treatment for breast cancer is preferentially administered in the order systemic chemotherapy followed by radiotherapy and then local regional chemotherapy. Perhaps, in the light of recent findings, this order of treatment application should be reconsidered. Local intra-arterial chemotherapy has proven to be effective as an induction treatment in breast cancer, and has been shown to reduce locoregional recurrences in breast cancer, with a higher response rate and tumour eradication rate than systemic chemotherapy and/or radiotherapy, particularly if the breast tissue has not been pre-irradiated [6]. It would therefore seem judicious to implement regional chemotherapy as an initial treatment of primary and locally recurrent breast cancer, with adjuvant systemic chemotherapy or radiotherapy being applied if no improvement occurs. However, it must be remembered that, to date, the number of patients enrolled

in studies utilising regional chemothe rapy in breast cancer has been small. Consequently, caution must be exercised when drawing conclusions from these data. Large, randomised clinical trials are required to assess more fully the efficacy of local regional chemotherapy in primary and locally recurrent breast tumours.

*Intra-abdominal cancers*

Intestinal

Despite advances in the treatment of intra-abdominal malignancies, therapeutic success is generally poor and treatment remains a common and unresolved problem. About 65% of patients with colorectal cancer develop hepatic metastases, which is the major cause of mortality in these patients. Surgical resection provides the only chance of cure, however, only a small proportion of metastases are deemed resectable. Even following resection, pelvic recurrence develops in 30% of patients, with a long-term survival of only 20-30% after 5 years [30, 44].

As with other cancers, treatment by systemic chemotherapy is associated with undesirable toxicity, which limits the administration of cytostatic drugs at their therapeutic concentrations. Regional chemotherapy has been implicated for advanced abdominal cancers, because, like the liver and breast, carcinomas occurring in this body region generally have a good blood supply. Indeed, many forms of regional treatment have recently been utilised in the treatment of a variety of advanced intra-abdominal cancers, including colon, pancreatic, intra-abdominal sarcoma, gyneco-urinary, stomach, and hepatobilary tumours.

One technique that is currently under investigation combines total abdominal perfusion (TAP) and aortic stop-flow in a method also known as 'Aigner's technique'. Use of Aigner's technique might be considered, for example, when a primary or recurrent bowel tumour with local or regional spread is encountered at the time of surgery; regional chemotherapy by TAP and stop-flow can be administered following resection of the tumour and necessary anastomosis. Only preliminary clinical studies have been undertaken utilising the Aigner technique. Despite the advanced nature of the tumours and the previous treatment failure in patients given this treatment strategy, it has been shown to induce a tumour response and to be relatively safe and effective in the reduction of tumour-associated pain [31]. To date, there is little clinical information available on the use of Aigner's technique and the healing of the anastomosis. However, a rat model has demonstrated that aortic stop-flow and intra-aortic chemotherapy do not affect anastomotic or bowel healing, and the presence of oxygen in the form of superoxide dismutase enhances anastomotic re-epithelisation [40].

The use of high-dose chemotherapy allied to chemofiltration is also being considered for use in locally advanced gastro-intestinal cancers [70]. Not only has tumour response been noted but also no nephrotoxicity or gastrointestinal-associated side effects were experienced [18, 70]. However, patient numbers in these studies were small, and caution should be exercised when drawing conclusions.

*Pancreatic cancer*

The 2-year survival rate of patients with adenocarcinoma of the pancreas is approximately 4%. Only about 15% of patients are candidates for resection at the time of diagnosis, and the 5-year survival rate following resection is approximately 7%. Palliative surgery does not effect survival time, which is, on average 3.4 months. These facts underline the importance of finding new ways of treating all types of unresectable pancreas carcinomas. The potential of using intra-arterial chemotherapy for the treatment of pancreatic tumours has been evaluated, and preliminary studies have demonstrated that pancreatic cancer is dose-dependently sensitive to regional chemotherapy.

Regional chemotherapy access to the tumour site is facilitated *via* the celiac axis and superior mesenteric arteries. Many variations in the application of this treatment are available, for example, the use of occlusive and embolic agents allied to the administration of a variety of cytotoxic agents. However, regional treatment of pancreatic tumours is still in its infancy and, moreover, the use of chemo-occlusion has been undertaken in only a small number of pilot studies. Nevertheless, results have been encouraging.

Several combination regimens which include regionally administered DSM have been utilised in the treatment of pancreatic carcinomas [1, 3, 5, 24]. In an initial study of 15 patients, celiac axis infusion of DSM and mitoxantrone, plus 5-FU and high dose mitomycin C with filtration, provided 4 complete responses (27%), 8 partial responses (53%) and 3 minor responses (20%). Similar results were reported for another study, in which 4/20 complete responses (20%), 12/20 partial responses (60%) and 3/20 minimal responses (15%) were recorded after DSM and mitoxantrone treatment [5].

In a more recent investigation, DSM-induced chemo-occlusion has been used alternately with stop-flow infusion in 4 monthly cycles, delivering mitomycin C and cisplatinum by bolus infusion into the celiac axis and superior mesenteric artery. This procedure was shown to be effective in inducing remission of pancreatic tumours, albeit that no extra benefit was provided by utilising both the celiac axis and superior mesenteric artery, as opposed to the celiac axis alone [24]. The temporary hypoxaemia induced by the aortic stop-flow infusion was also shown to enhance the activity of mitomycin C. Side effects experienced during this therapy were diarrhoea and abdominal discomfort in some patients after stop flow bolus infusion, however, bone marrow depression was not evident and DSM occlusion did not cause pain [24].

In a larger study of 164 patients with nonresectable,

locally metastasised pancreatic tumours, the efficacy of four different regional treatment regimens has been compared (Table III) [3]. Response criteria were tumour markers sampled every four weeks, a CT scan after 8 weeks and second look surgery at which the resectability of the tumour was assessed and biopsies taken. All four treatment regimens provided good clinical and histological response rates (78-100%) and differences between the four treatments, as assessed by clinical and histological response and survival, were small. It would seem, therefore, that regionally administered therapies can promote enhanced tumour response. So far, compared to historical controls, median survival has been prolonged in stage III and stage IV pancreatic cancer.

A substantial decrease in pain has been reported by patients after DSM administration. Indeed, more than 80% of patients receiving celiac axis infusion of DSM report almost complete resolution of pain. Moreover, the quality of life in responders is notably enhanced by the second cycle of treatment. The patient numbers were too small to identify a survival benefit, and it was concluded that patients with progressed stages of pancreatic cancer, for example, those with hepatosplenomegaly, extensive ascites and markedly reduced performance, were unlikely to experience a survival benefit from regional chemotherapy. Perhaps the criteria of efficacy based on survival should be reviewed and assessment be redefined according to specific tumour regression, enhanced quality of life and time to tumour progression.

It would seem, therefore, that pancreatic cancer responds to regional chemotherapy and patients with no or mild ascites may benefit from such treatment. There is recent evidence suggesting that the median survival rates may be improved, and marked improvements have been shown in the quality of life of these patients. As far as response was concerned, DSM has been described as an essential therapeutic factor in the treatment of pancreatic cancer. Indeed, if regional chemotherapy is undertaken *via* the celiac axis, DSM may aid in the reduction of the incidence of tumour progression. Furthermore, celiac axis infusion with DSM and cytotoxic drugs may reduce the possibility of a pancreatic tumour metastasising to the lymphatics and the liver. After such regional treatment, many patients with multiple lymph node and locally invasive tumour plus liver metastases have shown at second look surgery to have 90% regression of the liver metastases. Regional chemotherapy via the celiac axis would, therefore, seem to reach the pathways of the tumour in the upper abdomen, however, it does not reach the tumour in the lower abdomen.

The role of regional chemotherapy in the treatment of stage III/IV pancreatic cancer has recently been investigated in a prospective, randomised study, comparing intra-arterial *versus* systemic chemotherapy with mitomycin C, mitoxantrone and CDDP in both arms [4]. The intra-arterial arm received celiac axis infusion of mitoxantrone, mitomycin C, cisplatinum with DSM, and hypoxic abdominal perfusion with 20 mg of mitomycin C + 20 mg mitoxantrone. In this study, where there was no crossover, a more comprehensive assessment of the clinical benefits of such treatment was ascertained. In an early phase of the study there was already a significant advantage in survival in the intra-arterial group ($P = 0.003$), also as far as volume reduction of hepatomegaly ($P = 0.02$) and the course of bilirubin ($P = 0.001$) were concerned [4].

## Issues of current debate

### *Treatment order*

To date, regional chemotherapy has almost exclusively been applied in the treatment of recurrent tumours as a last option therapy, following the failure of conventional therapies to halt tumour progression. Several recent studies have, however, shown that regional chemotherapy provides substantial therapeutic benefit both when administered as an initial treatment in relapsed patients

**Table III:** Comparison of tumour response and survival in patients with metastasised pancreatic tumours treated with four regional treatment regimens (Aigner and Gailhofer 1993b).

| Group | Treatment | No patients total / evaluated | Response clinical / histological | Survival (months) |
|---|---|---|---|---|
| I | CAI (MMC, CDDP, 5-FU) | 27 / 27 | 78% / 90% | 12 |
| II | CAI (Mitoxantron, DSM) Chemofiltration (MMC) | 40 / 20 | 95% / 100% | 10 |
| III | CAI (MMC, CDDP, 5-FU, DSM) Aortic Stopflow (MMC) | 49 / 24 | 96% / 94% | 10 |
| IV | CAI (MMC, CDDP) Aortic Stopflow or Hypox. Perf. | 48 / 28 | 96% / 92% | 9.8 |

MMC = Mitomycin C, CDDP = Cisplatinum, 5-FU = 5-fluorouracil, DSM = Degradable starch microspheres, CAI = Celiac-axis infusion

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and in patients with hepatocellular carcinomas, and primary breast and intra-abdominal cancers.

At present, radiotherapy and surgical resection of a tumour are routinely administered in the treatment of breast, colo-rectal, pancreatic and liver cancer. Intra-arterial chemotherapy and chemofiltration are only utilised following radiotherapeutic treatment of local regional recurrence. Studies have shown, however, that the therapeutic efficacy of regional chemotherapy is reduced if it is administered following radiotherapy. The ability to administer effective regional chemotherapy would seem, therefore, to be precluded if radiotherapy is applied initially. There is thus little or no rationale for the current administration of radiotherapy and regional chemotherapy. However, mild doses of radiotherapy have been shown to increase the blood supply to the area being treated, therefore, low dose radiotherapy could be used as a supportive therapy, enhancing the efficacy of subsequent treatment with regional chemotherapy.

In the light of these findings it would seem prudent to apply regional chemotherapy prior to radiotherapy and/or surgical resection in the treatment of locally recurrent carcinomas. The potential of utilising regional chemotherapy to induce tumour necrosis, thus reducing the tumour size and so making it resectable, and hence promoting greater success with radiotherapy and surgical resection, has far reaching therapeutic benefits for liver, abdominal and pancreatic tumours.

It should also be remembered that locoregional treatment is important in the neo-adjuvant setting when vascularisation is still intact. Previously, regional chemotherapy has not been indicated in metastasising primary tumours of the liver, breast or abdomen. Recent studies have shown, however, that a combination of regional chemotherapy and resection of the primary lesion, followed by systemic chemotherapy, if systemic spread is indicated, offers the best chance of cure.

*Tumour spread*

If the prognosis of patients with pancreatic and gastric carcinoma is to improve then it is essential that the administration of regional chemotherapy fully encompasses all possible tumour sites and lymphatic involvement. Tumour spread in the abdomen is profoundly endemic, therefore, the most effective treatment regimen would be to treat the whole abdominal cavity. Recent studies tend to suggest that the addition of aortic stop flow and/or hypoxic perfusion following the administration of cytotoxic drugs into the celiac axis offer a therapeutic advantage. Microembolisation with DSM also appears to provide an advantage in response [2, 3].

It must be remembered that the highest rate of tumour regression and hence therapeutic benefit is achieved during the first 2 cycles of treatment with regional chemotherapy. Any additional treatment cycles seem to offer minimal additional benefits and thus put into question the necessity of multiple treatment cycles.

*Assessment of benefit*

To date, the treatment benefits experienced with regional chemotherapy have been assessed in terms of tumour response. The number of patients within any given study has been inadequate to allow an assessment of survival outcome. A reduction in tumour progression is, however, a prerequisite for an increase in patient survival. Whilst survival remains the ultimate endpoint, other factors should also be considered. The reduction in pain experienced by many patients following regional chemotherapy, particularly pancreatic carcinoma patients, is allied to improved patient quality of life. Systematic assessment of treatment benefits of regional chemotherapy in pancreatic cancer demonstrated an 80% decrease in the pain experienced, this decrease being immediately noticeable following the first cycle of treatment. Moreover, the ability to receive regional chemotherapy on an outpatient basis, without the need for extensive hospitalisation, is a substantial benefit to the patient. Finally, the reduced systemic toxicity and increased resectability of carcinomas following regional chemotherapy must also be viewed as a treatment benefit. Thus, until a survival benefit can be proved, treatment outcome might be more adequately defined by a combination of tumour response, time to local re-occurrence and quality of life, including a critical analysis of pain relief and disease free period.

## References


1. Aigner KR, Gailhofer S. (1991) Celiac axis infusion for locally metastasized pancreatic cancer using Spherex/mitoxantron microembolisation and mitomycin C/chemofiltration. Reg. Cancer Treat., 4: A2.
2. Aigner KR, Gailhofer S. (1993a) High dose MMC- aortic stopflow infusion (ASI) with versus without chemofiltration – a comparison of toxic side effects. Reg. Cancer Treat., Suppl.1: 3.
3. Aigner KR, Gailhofer S. (1993b) Regional chemotherapy for non-resectable, locally metastasized pancreatic cancer – four studies including 164 cases. Reg. Cancer Treat., Suppl.1: 2.
4. Aigner KR, Gailhofer S, Kopp S. Regional versus systemic chemotherapy with mitomycin and mitoxantron for locally advanced and metastasized pancreatic cancer – a randomised trial. Reg. Cancer Treat, in press.
5. Aigner KR, Gailhofer S, Müller H. (1992) Régional chemotherapy of advanced pancreatic cancer with mitoxantron-spherex and mitomycin C-chemofiltration. In: Klapdor (Ed) Tumor associated antigens, oncogenes, receptors, cytokines in tumor diagnosis and therapy at the beginning of the nineties. W. Zuckschwerdt Verlag München, Germany.
6. Aigner KR, Müller H, Chatzissavidis J. (1993) Subclavian artery infusion for locally recurrent breast cancer – a review on 144 patients. Reg. Cancer Treat., Suppl.1: 2.
7. Andersson M, Aronson KF, Balch C, Domellof L, Eksborg S, et al. (1989) Pharmacokinetics of intra-arterial mitomycin C with or without degradable starch microspheres (DSM) in the treatment of non-resectable liver cancer. Acta Oncol., 28: 219-222.
8. Asaishi K, Hayasaka H. (1989) Arterial infusion chemotherapy for breast cancer. Taguchi T, Nakamura H (ed) In Arterial infusion chemotherapy, Jpn. J. Cancer Chemother. Pub. Inc. pp 203-212.
9. Bleiberg H, Pector JC, Fruhling J, Parmentier N, Gerard B, Gordon