Regional Chemotherapy for Recurrent Platin Refractory Ovarian Cancer

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14.1 Introduction

The standard of care in the treatment of ovarian cancer is extensive cytoreduction, combined with platin-based combination chemotherapy such as Cis- or Carboplatin and Paclitaxel. Although this tumor is most susceptible to chemotherapy with response rates ranging between 70% and 80%, almost half of all patients who respond to initial treatment relapse within 2 years. The probability of achieving a second response after recurrence is closely correlated with the disease-free interval, such that the shorter the time to progression the lower chances of achieving a response to chemotherapy [1, 2].

In fact, most tumors that relapse within 6 months are platin refractory, they have the worst prognosis, treatment options are limited, and they are mostly considered noncurable [3]. Numerous attempts to overcome platin resistance, as by enhancing the dose of chemotherapeutics [4–10], high-dose chemotherapy [11, 12], or various combination therapies [13, 14] have failed to demonstrate any substantial benefit in terms of survival. However, along with increased tumor exposure toxicity is accentuated and may become intolerable.

To date, there are no cures in the recurrent setting and objective response rates hardly exceed 15%; recurrent platin refractory ovarian cancer still remains a challenge. With regard to studies that revealed response to dose intense therapies an increase of drug exposure might theoretically improve response as well as overall survival, but this is limited by exceeding toxicity. In the maintenance therapy phase III trial of 12 versus 3 cycles of paclitaxel [15, 16], indeed a favorable impact on progression-free survival (PFS) was noted in the 12 cycle patients but the study was discontinued at that point so that no final conclusion could be made regarding possibly prolonged overall survival. However, due to accentuated toxicity in terms of neuropathy the study did not establish clinical benefit in terms of quality adjusted survival.

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Based on the observation that an increased drug exposure might clearly affect residual disease and as a consequence improve clinical outcome, but must be limited because of accompanying toxicity, there is an urgent demand for an alteration in the modality or strategy of induction chemotherapy.

This was the rationale for investigating whether a further substantial increase of the administered drug concentration can be achieved by isolation perfusion techniques with an extracorporeal circuit. Such a system may generate a more intense drug exposure, strong enough to overcome chemoresistance and eradicate all or at least a significant proportion of the residual viable tumor cells, possibly including ovarian cancer progenitor stem cells [17].

In a controlled study of advanced and recurrent platin refractory FIGO III C and IV patients with ovarian cancer, the hypothesis that chemoresistance can be broken through with high drug exposure and avoiding or reducing side effects to a minimum by means of extracorporeal purification of blood was assessed [18].

14.2 Isolated Abdominal Perfusion

Isolation perfusion techniques are not new, but their practice has been limited.

There are two modalities of isolated perfusion of the abdomen. In the isolated setting with a heart-lung machine and an oxygenated extracorporeal circuit, perfusion time can usually be extended to 1 h when chemotherapeutics that develop optimal cytotoxicity under hyperoxic conditions are administered [19, 20].

The so-called hypoxic abdominal perfusion (HAP) takes advantage of the fact that a small number of drugs such as adriamycin and mitomycin, develop a multiple increase of cytotoxicity under hypoxic conditions (Figs. 14.1 and 14.2). Cisplatin, the basic drug in the treatment of ovarian cancer has no change in cytotoxicity whether used in hypoxic or hyperoxic medium [21].

14.3 Material and Methods

14.3.1 Technique of Hypoxic Abdominal Perfusion

Isolation of the abdominal segment and connection to an extracorporeal circuit is performed under general anesthesia. Through a small longitudinal incision in the groin the femoral or ileofemoral vessels are exposed below or above the inguinal ligament and secured with tapes and tourniquets. Through a longitudinal incision a venous stopflow catheter is inserted into the femoral vein and fixed with a prolene purse-string suture. The femoral artery is cannulated through a transverse incision (Fig. 14.3). Both stopflow catheters are placed with the balloon tips to the level of the diaphragm and the venous catheter just above the venous drainage of the liver veins into the vena cava (Fig. 14.4). After

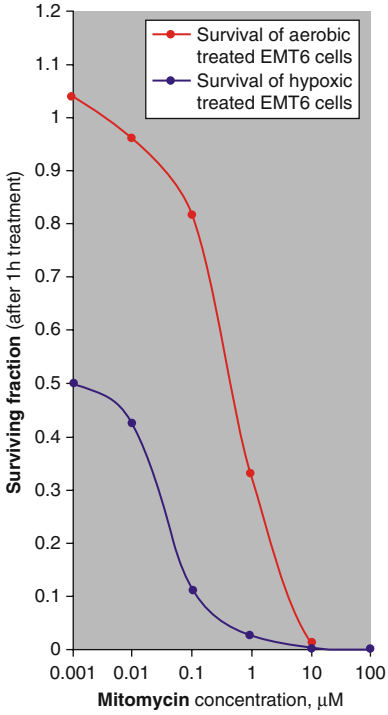

Fig. 14.1 Mitomycin toxicity to tumor cells in aerobic and hypoxic media [21]

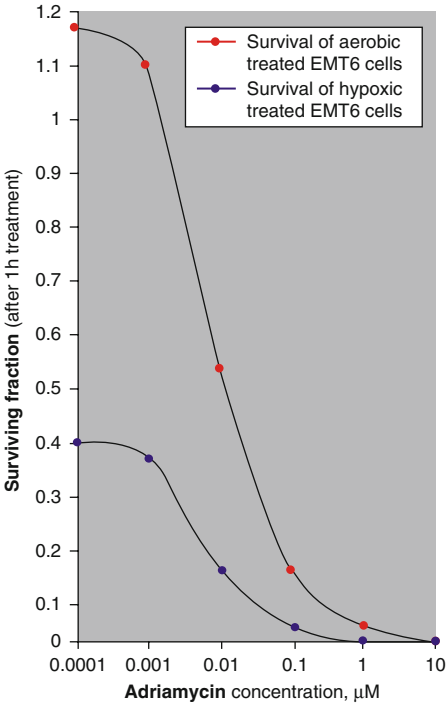

Fig. 14.2 Adriamycin toxicity to tumor cells in aerobic and hypoxic media [21]

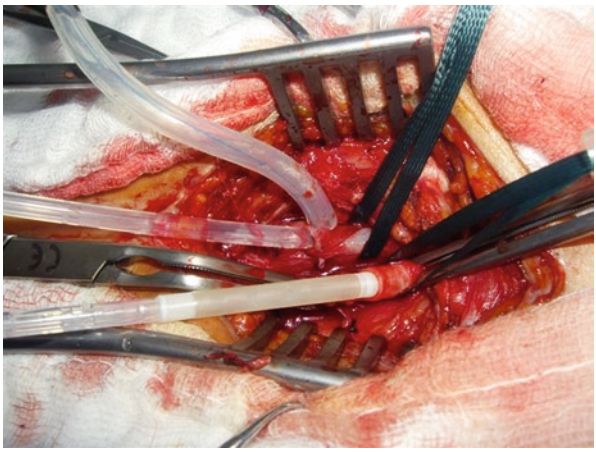

Fig. 14.3 Cannulation of the femoral vessels. The vein is cannulated and secured with a purse-string suture, the artery via a transverse incision and secured with a tape. The balloon is still visible outside the artery. Side holes below the balloon drain the larger channel of the three lumen stopflow catheter. A thinner channel serves to inflate the balloon and a second thinner channel allows to introduce a guide wire which exits at the tip of the catheter in order to smoothly proceed it in case of kinking of the pelvic vessels

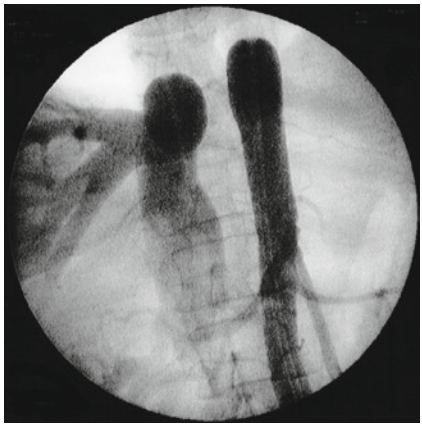

Fig. 14.4 Contrast imaging of the abdominal aorta and vena cava after inflation of both balloons with saline and contrast medium and injection of contrast medium through the side holes in the major channel of the three lumen stopflow catheter

correct positioning, both catheters are deflated again in order to avoid too early hypoxia in the abdominal segment. To temporarily block venous return from the lower limbs two pneumatic cuffs placed around the upper thighs are then inflated. After starting the extracorporeal circuit at a flow rate of maximally 500 mL/min, the chemotherapeutics are administered as a 1–2 min bolus infusion into the arterial line. Immediately after injection both stopflow catheters are blocked and the extracorporeal circuit maintained for 15 min of hypoxic perfusion (Fig. 14.5). Because of subsequent chemofiltration, leakage control

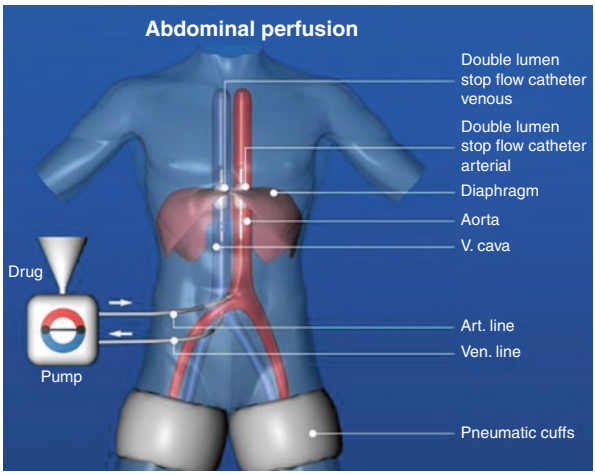

Fig. 14.5 Scheme of hypoxic abdominal perfusion. The major channels of the aortic and vena cava stopflow catheter are connected to an extracorporeal circuit. After a 15 min exposure to cytotoxics balloons are deflated and chemofiltration through the same catheters is started

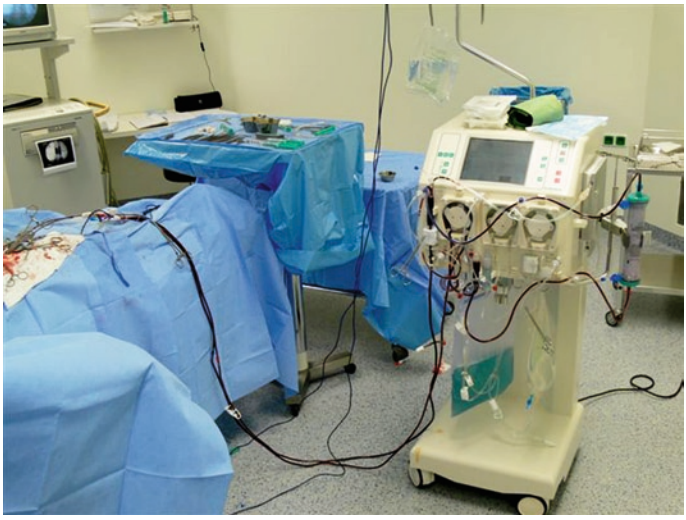

Fig. 14.6 Chemofiltration after local drug exposure. The arterial and venous lines are exited from the groin and connected to the chemoprocessor

in the isolated circuit is not necessary. Thereafter both stopflow catheters are unblocked simultaneously and chemofiltration through the same catheters is commenced (Fig. 14.6) and run at a maximum speed of 500 mL/min for substitution of a minimum of 4 L of filtrate. It has been shown in a comparative study of intra-aortic chemotherapy with versus without chemofiltration that post-therapeutic chemofiltration prevents plasma peak concentrations and exhibits a favorable effect by reducing immediate toxicity and postponing cumulative toxicity in patients treated with isolated perfusion techniques [22, 23]. After the procedure, the catheters are removed and the vessels repaired with running sutures.

14.4 Treatment Protocol

Four cycles of isolated hypoxic abdominal perfusion are performed at 4 weeks intervals each. The drugs administered are Cisplatinum, Adriamycin and Mitomycin [18]. After each treatment cycle a complete blood count and a platelet count were carried out on a weekly basis. CA 12-5 levels were tested directly before each cycle and on day 5 before discharging the patient. A CT scan was performed after the second and the fourth therapy.

Patients who had given informed consent underwent explorative second-look laparotomy for re-staging and determination of histological response. Special attention was given to responses of the tumor-marker CA 12-5 during the entire therapy, especially when there was a beneficial effect on the patient's performance findings such as reduction or resolution of ascites and symptom-free survival.

Exclusion criteria were severe concurrent malignancies or other health problems such as cardiovascular insufficiency from coronary heart disease or absolute arrhythmia or uncontrolled diabetes or severe infection. White blood count should not be below 2,500/μL and not in a decreasing tendency, platelets not lower than 150,000/μL. Drugs were chosen according to the preferential toxicity under hypoxic conditions (Figs. 14.1 and 14.2) as lined out by B. Teicher [21].

Patients were mainly FIGO III C (71%) and FIGO IV (25%). Seventy-eight point five percent had a 4-Quadrant peritoneal carcinosis and interestingly 39% (n = 31 patients) were histologically grade G3 (Table 14.1). Seventy-nine percent of all patients were heavily pretreated, six had had third-line and one fourth-line therapy [18].

14.5 Results

Endpoints of the study were quality of life, survival, and response. Clinical response from decrease of the tumor-marker 12-5, CT scan, and quality of life especially in terms of decrease or resolution of ascites, pain, and discomfort was an overall 64% compared to 48% histological response from second-look surgery. A complete resolution of ascites was noted in 43% of the patients after two treatments and a further 19% revealed a marked

Table 14.1 Patient characteristics

Stage	FIGO IIIb	4% (n = 3 patients)
	FIGO IIIc	71% (n = 56 patients)
	FIGO IV	25% (n = 20 patients)
Peritoneal carcinosis	4-quadrant	78% (n = 62 patients)
	2-quadrant	21.5% (n = 17 patients)
Grading	G3	39% (n = 31 patients)

decrease of the volume by estimated more than 50%. Three out of four patients (74%) reported a definite relief of pain and improvement of abdominal discomfort (Table 14.2). Medium progression-free survival was 8 months and medium overall survival was 14 months. Eight patients survived between 6 and 18 years. Out of four patients surviving between 10 and 18 years three initially had G3 tumors. There was no statistical difference in survival curves of pretreated compared to non-pretreated patients (Fig. 14.7).

Table 14.2 Results

Response			
Clinical	CR 25%	PR 39%	Total 64%
Histological	CR 13%	PR 35%	Total 48%
Ascites			
Resolution	43%		Total 62%
Reduction	19%		
Survival (%)	**PFS (months)**		**Overall (months)**
25	12		30
50 (median)	8		14
75	4		8

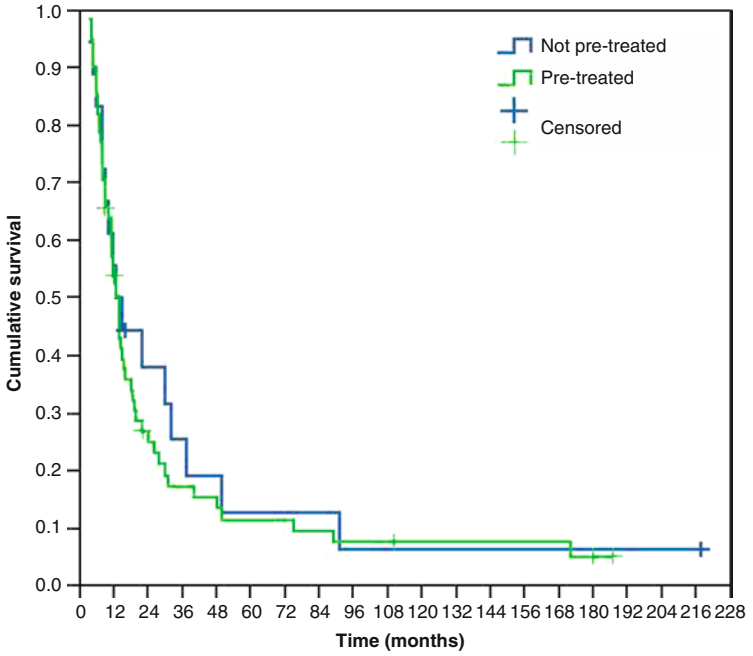

Fig. 14.7 Kaplan-Meier survival estimate of hypoxic abdominal perfusion for pretreated (n = 63) versus non-pretreated (n = 17) FIGO III/IV advanced ovarian cancer

14.6 Toxicity

Bone-marrow toxicity was usually mild and ranged between grade 1 and 2, except those patients with a heavy prior exposure to third- or fourth-line chemotherapy where grade 3 leucopenia and thrombocytopenia was noted. Grade IV toxicity was never observed. Fatigue was usually associated with post-therapeutic tumor necrosis causing an initial steep increase of LDH and CA 12-5. This syndrome is most commonly observed during the first post-therapeutic week, predominantly on post-op day 2 and 3 in about 15–20% of the patients. The predominant clinical symptom in those patients was fever and fatigue.

14.7 Discussion

The crucial point in the treatment of ovarian cancer is that, whatever drug combination aside of the standard of care – cisplatin and paclitaxel – has been used did not translate into real overall improvement of progression-free survival (PFS), overall survival (OS), or quality of life (QoL). The crux in either studies such as prolonged, dose-dense, or high-dose chemotherapy was toxicity, like neuropathy (hand-foot-syndrome), neutropenia, alopecia, or fatigue. In addition, the lack of formal quality of life assessments in most studies prevented conclusions on quality adjusted survival. In view of the fact that specific mortality from ovarian cancer has hardly changed over the past three decades, it seemed reasonable to investigate other treatment options. Since ovarian cancer is one of the most angiogenic neoplasms with extended new vasculature, targeted therapies, affecting the blood supply of neoplasms hopefully would solve the problem by achieving an antitumor response while largely sparing damage to healthy tissues. However, apart from clinical effects, mostly in terms of prolonged PFS, severe toxic effects like hypertension, hemorrhages, proteinuria, cardiotoxicity, and gastrointestinal toxicity with perforations were noted [32].

In a study on 32 patients who had multiple prior chemotherapies good results were reported with Bevacizumab [24]. The median survival time of 6.9 months at a median PFS of 5.5 months, however, was far less than those after isolated abdominal perfusion with a median survival time of 14 months and a PFS of 8 months. In a phase II study to assess the efficacy and tolerability of Bevacizumab, a median PFS and overall survival of 4.7 months and 17 months, respectively, in patients with progressive ovarian cancer was reported. Toxicity and adverse events were noted grade III (hypertension) and grade IV in terms of pulmonary embolism, vomiting, constipation, and proteinuria [25]. Although data seem promising, toxicity and side effects are definitely greater than after isolated perfusion and chemofiltration.

The upfront goal in any medical or surgical cancer therapy should be to enable patients to live longer and to provide them a better quality of life. There are essentially no other universally agreed upon reasons for recommending or initiating a therapy [26]. Yet, thousands of patients have been treated in multiple trials [4–14] that failed to disclose any substantial progress especially not in quality of life adjusted survival. Just as sometimes

surgical debulking in advanced disease prolongs PFS, this is limited to early stages when so-called curative surgery is feasible [27].

Unfortunately, most treatment regimens yield improvement of PFS but at the cost of greater toxicity, presupposing that prolonged PFS predisposes to prolonged overall survival. This is not always so, but a prolonged overall survival is almost always associated with an advantage in PFS.

As it seems, progress in therapies of different cancers like ovarian, colorectal, or testicular cancer is largely correlated to the chemoresistance of tumor stem cells. While cure rates have risen dramatically for testicular cancer (from 23% to 81%) and stage III colorectal cancer (from 29% to 47%) during the last three decades [17], the cure rate for ovarian cancer has changed only little, from 12% to 14% during the same time period. The relatively small cure fraction in ovarian cancer patients might be due to a relative insensitivity of epithelial ovarian cancer stem cells with the overall survival benefit accruing instead from the reduction in the non-stem cell compartment of the tumor. This might explain why after relapse a salvage treatment can be administered which results in a renewed tumor control and may prolong survival [26]. Such a strategy might expose patients to less toxicity. The problem of chemoresistant stem cells however remains, and those patients have only limited choices available. A basic principle to avoid systemic "drug spill" and to increase drug activity at the target site is the access via the arterial blood supply of tumors taking advantage of the first pass extraction of chemotherapeutics [28–31]. The isolation perfusion technique may generate adjustable drug exposures (area under the curve, AUC) and possibly break through drug resistance of tumor stem cells. Subsequent chemofiltration dramatically reduces side effects and patients generally report a good quality of life. In the reported isolation perfusion trial interestingly continuing survivals over many years have been achieved even in highly malignant G3 tumors, and the most important aspect is that those patients had an associated improvement in quality of life adjusted survival. Substantial improvements of abdominal pain and discomfort in 74% and complete resolution of ascites in 43% are features of utmost importance. This is a considerable improvement as the majority of patients in this study presented with far advanced disease, still suffering from residual side effects of prior systemic chemotherapies and a burden of ascites, having a life expectancy of some 6–12 weeks.

Quality of life is a parameter in cancer therapy that deserves predominant consideration, foremost since new therapeutic options provide an increase of PFS or survival – if any – of 1 or 2 or 3 months at the cost of considerable toxicity and increased financial burden. Therefore, a phase III trial comparing regional chemotherapy in terms of isolation perfusion with current conventional treatments is recommended.

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