Hypoxic Abdominal Perfusion for Recurrent Platin Refractory Ovarian Cancer

Research Article

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Abbreviations: progression free survival (PFS)

Abstract

In platin-refractory recurrent ovarian cancer the evidence available does not support firm conclusion about the preferred chemotherapy regimen. An increase of local exposure, however, by means of isolation perfusion techniques may breakthrough drug resistance and prolong symptom-free survival and overall survival.

In a study on 79 patients, 61 of which were platin-resistant and in progression after first and second line platin combination chemotherapies, isolated hypoxic abdominal perfusion was performed.

20 complete responses and 31 partial responses were registered for an overall response rate of 64 %. Complete resolution of ascites after two isolated perfusions was noted in 43 %, a reduction of the ascites by > 50 % was observed in 19 %. Bone marrow toxicity was usually mild and did not exceed grade 1 – 2. Grade 3 leucopenia and thrombocytopenia was only observed in cases with intensive prior systemic chemotherapy. The median survival time was 14 months, the median progression free survival was 8 months and the 25 % survival was 30 months at predominantly good quality of life. 8/79 patients (10 %) survived six years and more (75, 89, 91, 110, 172, 180, 187, 218 months). 4/79 patients have been living disease free for 110, 180, 187 and 218 months. Three of them had G3 tumors.

I. Introduction

Platinum refractory recurrent ovarian cancer remains a challenge. Currently the treatment of choice for advanced disease involves thorough cytoreductive surgery in combination with platinum containing chemotherapy plus paclitaxel. In case of relapse the prognosis is closely correlated with the interval from completion of initial therapy to recurrence (Gore M. E. et al, 1990), such that, the longer the interval between primary treatment to relapse, the greater the chance to have response rates to retreatment approaching those achieved with primary therapy. Therapeutic options, however, are poor in those patients who relapse within six months following completion of primary therapy, because their tumors are most unlikely to respond to any kind of therapy. These patients are considered non curable (Ozols R. F., 1997).

In studies on long-term maintenance therapy (Markman M. et al, 2003) or enhanced dose chemotherapy (Dark G. G. et al, 2005) a prolonged remission was noted, but without any improvement in overall survival. The reason for this phenomenon might be that a much higher local drug exposure is required in order to definitely affect residual disease and as a consequence improve overall survival. This was the rationale to investigate whether a further, substantial increase of the administered drug concentration, as can be achieved by isolated perfusion with an extracorporeal circuit, may generate a drug-exposure, strong enough to eradicate the entire or at least part of the residual drug-resistant tumor burden.

II. Material and Methods

Patient characteristics. 79 patients in clinical stage FIGO IIIC/IV were enrolled in this phase II clinical trial. 61 were in progression after first and

second line chemotherapy with cisplatin combination therapies (anthracyclines, cyclophosphamide, taxanes). Six patients had had third line, one fourth line pre-treatment. One patient had prior radiotherapy of the pelvis (Tab. 1). Median age was 55 years (30 – 83 years). Three patients were stage FIGO III B (4 %), 56 patients were FIGO III C (71 %) and 20 patients (25 %) were stage FIGO IV disease. 62 patients (78.5 %) had a four-quadrant peritoneal carcinosis and 17 patients (21.5 %) a two-quadrant dissemination. Tumor grading was noted grade G3 in 39 % of the patients (Tab. 2). Pre-treatment data are listed in Tab. 2. 62/79 patients had been pre-treated. 54 of those pre-treated patients had prior systemic chemotherapy (87 %), four had radiochemotherapy (6.5 %) and the remainder had radionuclidinstallation and systemic chemotherapy (5 %) and radiotherapy of the pelvis (1.5 %).

Table 1. Patient Characteristics I

Pretreatment	**n = 62/79 (79 %)**
Systemic chemotherapy	n = 54/62 (87 %)
Radiochemotherapy	n = 4/62 (6,5 %)
Radionuclid install. + SCT:	n = 3/62 (5 %)
Radiotherapy pelvis:	n = 1/62 (1,5 %)

Table 2. Patients Characteristics II

Age:	55 years (range: 30 – 83)		
Stage:	FIGO III B:	3 patients	(4 %)
	FIGO III C:	56 patients	(71 %)
	FIGO IV:	20 patients	(25 %)
	4 – quadrant peritoneal carcinosis:	62 patients	(78,5 %)
	2 – quadrant peritoneal carcinosis:	17 patients	(21,5 %)
Grading:	G3: 39 %		

Technique of perfusion and chemofiltration. Isolated abdominal perfusion is performed in general anesthesia. Through a small longitudinal incision in the groin the femoral or ilio-femoral vessels are exposed beneath the inguinal ligament and secured with 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. Both stopflow-catheters (Pfm Cologne, Medipoint Hamburg) are proceeded with the balloon tips to the level of the diaphragm, the venous catheter just above the venous drainage of the liver veins into the vena cava. After correct positioning both catheters are deflated again in order to avoid too early hypoxia. Two pneumatic cuffs around the upper limbs are then blocked. After starting the extracorporeal circuit at a flowrate of maximally 500 ml/min, the chemotherapeutics are administered as a one minute bolus infusion into the arterial line. Immediately after injection both stopflow-catheters are blocked and the extracorporeal circuit maintained for fifteen minutes of hypoxic perfusion (Fig. 1). Thereafter both stopflow-catheters are deblocked simultaneously and chemofiltration through the same catheters is switched on (Fig. 2) for substitution of approximately four liters. After the procedure the catheters are removed and the vessels repaired with running sutures.

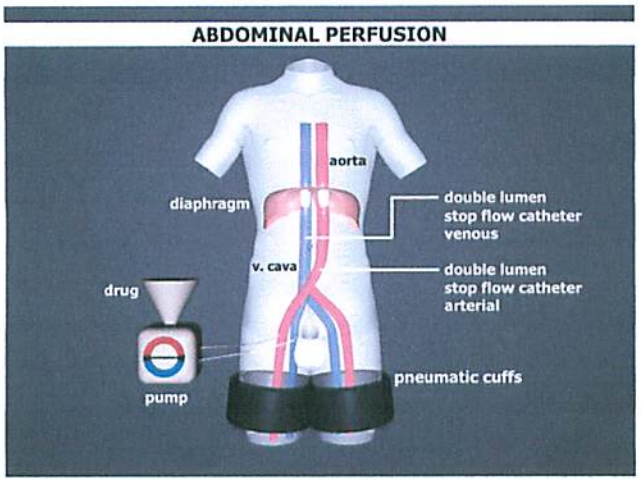

Figure 1. Scheme of Perfusion

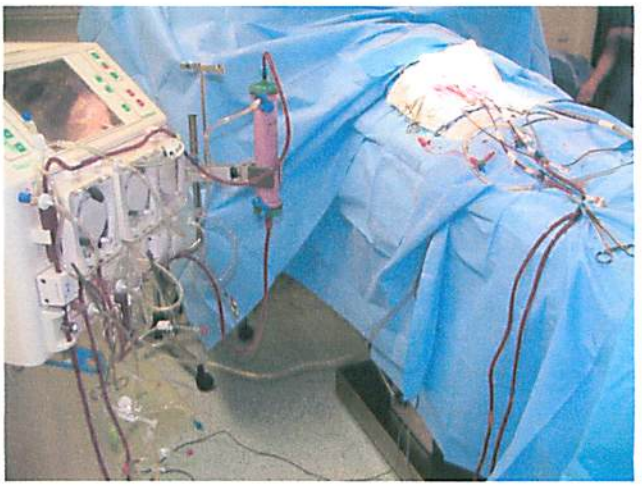

Figure 2. Chemofiltration

III. Treatment

Four cycles of isolated hypoxic abdominal perfusion were performed in four weeks intervals. The doses administered into the arterial line of the perfusion circuit were cisplatinum 1 mg/kg, adriamycin 07. mg/kg and mitomycin 0.43 mg/kg bodyweight. After each treatment cycle complete blood count and platelet count were carried out on a weekly basis. CA 12-5 levels were tested on day one of each cycle, directly before starting the isolated perfusion and on day 5 before discharging the patient. A CT-scan was performed after the second and the fourth cycle. 23/79 patients underwent explorative second look laparotomy for re-staging and determination of histological response. Clinical response was evaluated after the second and the fourth treatment cycle. Complete response (CR) was defined as the disappearance of all target lesions in CT-scan, normalization of the tumor marker CA 12-5 lasting at least four weeks and improvement of quality of life to "symptom free survival". Partial response was defined a 30 % or greater reduction of the longest diameter of target lesions, if accessible, and a more than 50 % reduction of the tumor marker CA 12-5.

Exclusion criteria were severe concurrent malignancies 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/nl and not in a decrease, platelets above 150.000/nl. Choice of drugs in combination with hypoxia was according to Beverly A. Teichers (1981) classification of antineoplastic agents by their selective toxicities toward oxygenated and hypoxic tumor cells. Herein mitomycin C and adriamycin were preferentially toxic under hypoxic conditions (Fig. 3, 4), whilst cisplatinum did not show any major preferential toxicity to cells under the condition of oxygenation or hypoxia.

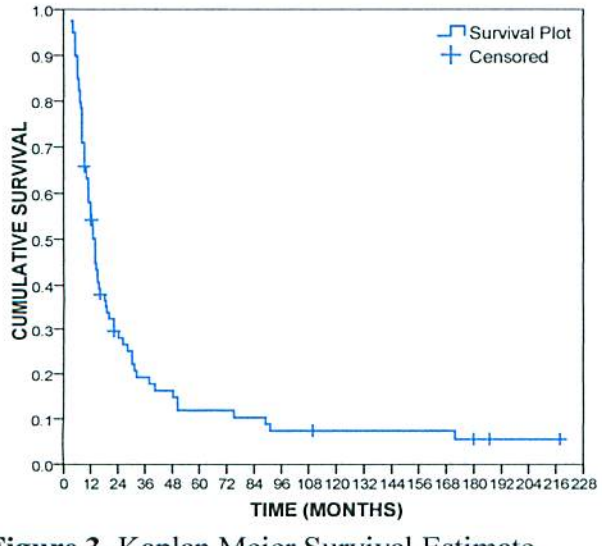

Figure 3. Kaplan Meier Survival Estimate

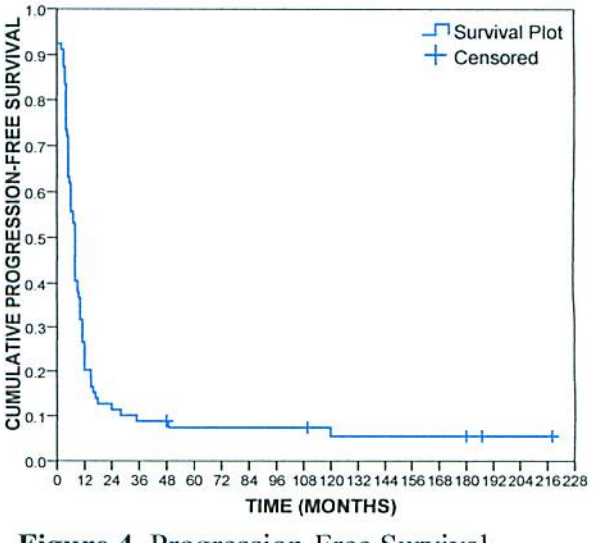

Figure 4. Progression-Free Survival

IV. Results

Histological response as an objective criterion was evaluated in 23 patients who underwent second-look laparotomy for restaging.

Clinical response was estimated according to the course of the tumor marker CA 12 – 5, the CT-scan, and the performance and quality of life, especially in terms of decrease or resolution of ascites, pain and discomfort. Special attention was given to symptom free survival.

The rate of complete remissions, comparing clinical versus histological response was 25% vs. 13 %. The rate of partial remissions was 39 % vs. 35 %, respectively.

In the overall series 51 clinically complete and partial remissions (64 %) were noted, whereas overall histological CR's and PR's were 48 % (Tab.3).

Complete resolution of ascites was observed in 43% of the patients after two therapies, and a marked reduction by estimated more than 50 % of the prior volume was noted in 19%. This translates into a clinical response in terms of ascites in 62 % of all patients (Tab. 4).

Approximately three out of four patients (74 %) reported a substantial release of pain and abdominal discomfort.

Median survival time of all 79 patients was 14 months, whilst the 25 % survival amounted to 30 months. Median progression free survival was 8 months (Tab. 5).

Eight patients survived six years and more (79, 89, 91, 110, 180, 187, 218 months), in other words, 10% of all patients survived between six years and seven months up to eighteen years and two months.

The remaining four survivors have been living disease and symptom free for 110, 180, 187 and 218 months. Three of them initially had G3 tumors.

Table 3. Response Rates Clinical-Histological

1. Clinical Response		**2. Histological Response**	
CR:	20/79 Pat. = 25%	CR:	3/23 Pat. = 13%
	64%		**48 %**
PR:	31/79 Pat. = 39%	PR:	8/23 Pat. = 35%

Table 4. Response Ascites

Results		
Resolution of Ascites	43 %	
		62 %
Reduction > 50 %:	19 %	

Table 5. Progression-Free Survival

	PFS (months)	**Survival (months)**
25 %	12	30
50 %	8	14
75 %	4	8

Toxicity and side-effects. The most common side-effects are lymphfistulas (> 30 %) in the groin, such as a daily secretion between 30 ml to 70 ml or more, lasting between two days or two weeks until they dry up. Bone marrow toxicity was usually mild and did not exceed grade 1 – 2, except in patients with intensive prior third or fourth line chemotherapy. In these patients grade 3 leucopenia and thrombocytopenia was observed. Grade 4 toxicity never occurred. Fatigue was observed in coincidence with posttherapeutic peak increase of the LDH and CA 12 – 5, lasting two to three days and was considered a sign of tumor destruction or tumor lysis syndrom. Those patients (15 – 20 %) usually develop fever in the afternoon during the first postoperative week.

V. Discussion

A number of randomized studies in the past have failed to prove a clear superiority of any one chemotherapeutic regimen, neither in survival, nor in response rate or quality of life (Fung Kee Fung M. et al 2002) only relapses occurring after a progression free survival of more than one year were successfully treated and responded to docetaxel and oxaliplatin (G. Ferrandina et al., 2007). Just as little, surgical debulking in advanced disease prolongs progression free survival. This is limited to early stages where curative surgery is feasible (Crawford et al, 2005).

In an attempt to break through drug resistance, a number of trials with dose intensification were conducted (Dark G. G. et al, 2005; Omura G. A. et al, 2003). Despite increased response rates they did not translate into prolonged survival but exhibited more toxicity. In context with recent studies toxicity was the limiting factor for dose escalation.

Continuing dose escalation by means of maintenance therapy with paclitaxel for an extended time period in women with advanced ovarian cancer who had achieved a clinically defined complete response to initial platinum/paclitaxel- based chemotherapy significantly prolonged progression free survival but did not establish clinical benefit in terms of prolonged survival nor quality adjusted survival due to severe neuropathy which again, forced to reduce dosages (Markman, M. et al, 2003). After dose escalation turned out to be a dead end street other therapeutic modalities like Vascular Endothelial Growth Factor (VEGF) inhibitors with our without accompanying chemotherapy were considered to be promising treatment options.

Monk BJ et al (2006) report good results with Bevacizumab in a study on 32 patients who had multiple prior chemotherapies. The median survival time of 6.9 months at a median progression free survival (PFS) of 5.5 months, however, was far beyond 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 Burger R. A. et al (2007) reported a median PFS and overall survival of 4.7 months and 17 months respectively in patients with progressive ovarian cancer. Toxicity and adverse events were noted grade 3 (hypertension) and grade 4 in terms of pulmonary embolism, vomiting, constipation and proteinurea. Although data seem promising, toxicity and side-effects are higher than after isolated perfusion and chemofiltration. Garcia A. A. et al (2008) reported similar results with a somewhat longer PFS (7.2 months) and about the same overall survival (16.9 months). Toxicity included gastrointestinal bleeding, perforation and pulmonary hypertension.

It has to be pointed out, however, that due to inhomogeneous patient selection phase II studies cannot be compared. Therefore it seems mandatory to initiate a randomized phase III trial comparing the isolation perfusion access with other modalities.

The remaining option, high dose chemotherapy, was investigated by V. Moebus et al (2007) in a phase III study, comparing high dose chemotherapy with peripheral blood stem cell support with standard intravenous chemotherapy for first line treatment of advanced ovarian cancer. In this study toxicity was much higher in the high dose chemotherapy arm, yet it failed to improve survival. Although disappointing at the first glance, these data are important (Ozols R. F., 2007) because they make favourable results from prior phase II studies on substantial benefit from high-dose chemotherapy appear questionable. There seems to have been an over-interpretation of positive results which possibly to a great extent depend on patient selection criteria. (Markman, M. et al 2003, Dark G. G. et al 2005, Omura G. A. et al 2003, Levin L., Hrynink W. M. 1987, Jodrell D. I. et al 1992, Thigpen J. T. 1997).

Another crucial point in the interpretation of dose-response behaviour is the absolute drug-concentration required to overcome drug-resistance. In this aspect isolation perfusion techniques are a much more flexible tool, because required concentrations and AUC's can be adjusted more or less on demand. The upper dose- or concentration limit is not systemic

toxicity, but local tissue tolerance in the isolated circuit.

In this study with regional chemotherapy the starting point and the treatment modality differ from other studies. First, patient selection included all patients in whom chemotherapy had been abandoned due to non responsiveness or patients who refused further chemotherapy due to intolerable toxicity. Second isolation perfusion is different from high-dose chemotherapy insofar as higher exposures (AUC's) are feasible because of segmental treatment and subsequent chemofiltration which cuts off peak concentrations of the systemic drug exposure after deblocking the balloon catheters and cuffs. Furtheron the administration of the total drug into the arterial line of the perfusion system can generate a much higher arterial drug concentration than can be achieved with sequential intravenous high-dose chemotherapy and thus establish a first pass tissue extraction able to overcome drug resistance. An important parameter was the administration of adriamycin and mitomycin which develop increased cytotoxicity under hypoxia (B. A. Teicher et al 1981) whereas cisplatinum shows no preferential toxicity under either conditions.

The most important moment while performing a hypoxic isolated perfusion, is time of administration of the chemotherapeutics into the arterial line. It is a crucial error to wait with the application until the perfusion system is in a stable balance and then infuse the drug over a longer time interval (van Jiken M.G. et all 2005). In a hypoxic system at a low pH drugs are most unlikely to pass cell membranes. This may be the reason for unfavourable results (Meyer F. et al 2006).

In a recent phase II study, Pohlen U. et al (2007) report positive results with hypoxic abdominal perfusion in 59 patients with intraabdominal tumors like colorectal-, stomach-, gallbladder- and pancreatic cancer – all of them more chemoresistant than ovarian cancer. Nevertheless with 22 partial responders a good result was obtained.

If chemotherapeutics are applied in the given doses, the risk of bone marrow toxicity is very low, even if there is a systemic leakage and systemic drug exposure after opening the isolated circuit. Peak drug concentrations are eliminated by means of subsequent chemofiltration. Thus toxicity acceptable and quality of life is not impaired, but improved (Tonn J. C., 1985, Muchmore J. H. et al 1995, Aigner K. R. 1983, Aigner K. R. 1985, Aigner K. R. 1988). Hypoxic perfusion, although performed as a routine since 17 years has definitely one weak point. This is the short time interval, available for injection of drugs at an acceptable pH, which is only a few minutes. Advantage of increased cytotoxicity under hypoxia can only be taken after the drug has entered the tumor tissue- and this requires initial oxygenation. Isolated abdominal perfusion with chemofiltration is also feasible using a heartlungmachine. Although technically more sophisticated, with sufficient routine and experience it is performed with the same manpower and with 1 ½ - 2 hours not more time consuming than hypoxic perfusion. Expanding the interval of oxygenation by a few minutes might improve the outcome.
However, only phase III trials can give a clear answer about the real value of a method. Since even in G3 tumors continuing survivals over many years have been achieved, a phase III trial comparing regional chemotherapy in terms of isolation perfusion with current conventional treatments is recommended.

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