Regional Chemotherapy in Recurrent Platinum-Refractory Ovarian Cancer

24

Karl Reinhard Aigner and Sabine Gailhofer

24.1 Introduction

The standard therapy with peritoneal metastatic ovarian cancer is extended cytoreduction, associated with combination chemotherapy based on platinum such as cisplatin or carboplatin and paclitaxel. Even though this tumor is very chemosensitive and the response rates range between 70 % and 80 %, recurrence appears within 2 years in almost half the patients who respond to the initial treatment well. The likelihood of a second response to chemotherapy after a recurrence is closely correlated with the recurrence-free interval. The shorter the time interval is to tumor progression, the less likely are the chances of a response to further chemotherapy [1, 2].

If a recurrence happens within 6 months, it is usually associated with a poor prognosis and the range of treatments available is very limited. A curative treatment is no longer possible [3]. Various attempts to overcome platinum resistance, such as increasing the dose [4–10], high-dose chemotherapy [11, 12] or various combination therapies [13, 14], were incapable of achieving any really relevant clinical survival advantage. Toxicity and side effects, however, are significantly worse under increased exposure to cytostatic agents and often intolerable.

Currently there is no cure for recurrent ovarian cancer, and objectively measurable response rates hardly exceed the 15 % limit. The treatment of platinum-resistant ovarian cancer continues to be a challenge. In relation to the studies, which could show an increase in response rate following dose-intensified therapies, an improvement in response and overall survival rates could be achieved in theory with an increase in exposure to cytostatic agents. However, this option is very limited due to its excessive toxicity. In a phase-III trial on maintenance therapy of 12 versus three

K.R. Aigner, MD (✉) • S. Gailhofer
Department of Surgical Oncology, Medias Klinikum GmbH & Co KG,
Krankenhausstrasse 3a, Burghausen 84489, Germany
e-mail: info@prof-aigner.de

K.R. Aigner, F.O. Stephens (eds.), *Induction Chemotherapy,*
DOI 10.1007/978-3-319-28773-7_24

cycles of paclitaxel [15, 16], a clearly positive influence on progression-free survival among patients with 12 treatment cycles was observed. However, the study was canceled at this point so it was ultimately impossible to come to any conclusion about potentially prolonging overall survival. Due to the strong increase in toxicity in the form of neuropathies, the study was incapable of demonstrating any clinical benefit in terms of survival with quality of life.

Based on the observation that an increase in drug exposure is accompanied by an increased cytotoxic effect and consequently the clinical result could improve but is limited by the accompanying toxicity, there is an urgent need for a change or improvement in induction chemotherapy.

Based on this finding, it was an obvious step to investigate whether a further significant increase in the administered concentration of cytostatic agents could be achieved with an isolated perfusion procedure with extracorporeal circuit. Such a system is capable of generating a significantly higher cytostatic exposure, strong enough in some cases to break through chemoresistance and destroy all or at least a considerable amount of the residual tumor cell groups, possibly even tumor stem cells [17].

The hypothesis that chemoresistance could be breached with high drug exposure and that side effects could be minimized or prevented by extracorporeal chemofiltration at the same time has been investigated in a controlled study of patients with advanced and recurrent platinum-refractory FIGO IIIc and IV ovarian cancer [18].

24.2 Isolated Abdominal Perfusion

Isolated perfusion techniques are not new, but their clinical use has been limited so far.

There are two forms of isolated abdominal perfusion. In the perfusion system with a heart-lung machine and oxygenated extracorporeal circuit, the perfusion time may be extended to an hour and more, if cytostatic agents with increased cytotoxicity are used with hyperoxygenation [19, 20].

What is known as hypoxic abdominal perfusion (HAP) uses the increased cytotoxicity of several chemotherapeutic agents such as adriamycin and mitomycin under hypoxic conditions (Figs. 24.1 and 24.2). Cisplatin as the base substance in treating the ovarian cancer is equally effective under hypoxic as well as hyperoxic conditions [21].

24.3 Material and Methods

24.3.1 Technique of Hypoxic Abdominal Perfusion

The isolation of the abdominal segment in connection with an extracorporeal circuit is carried out under general anesthetic. A small longitudinal incision in the groin exposes the femoral or iliofemoral blood vessels below or above the inguinal

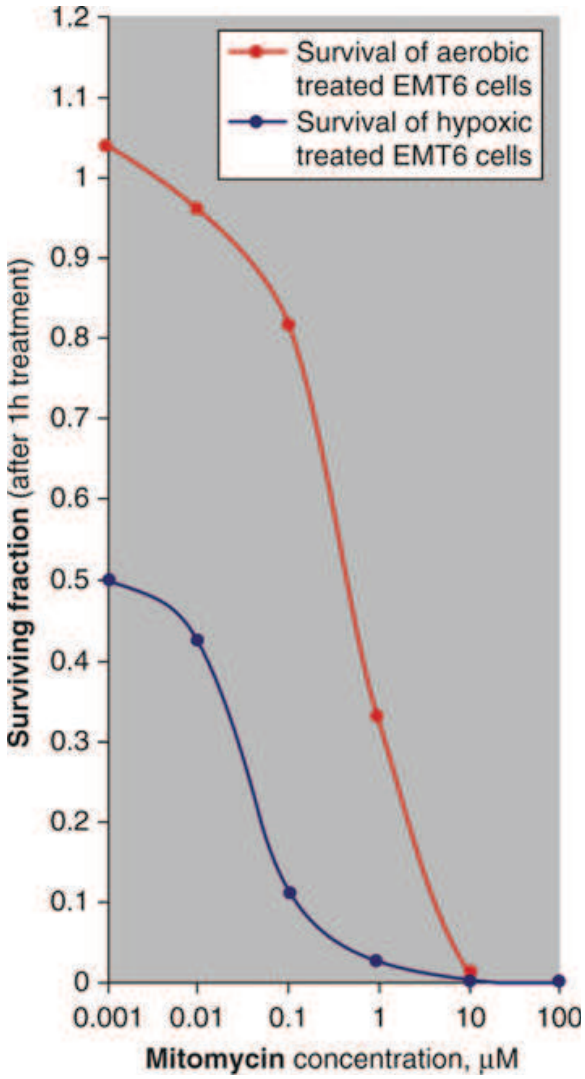

Fig. 24.1 Mitomycin toxicity to tumor cells in aerobic and hypoxic media [21]

ligament, and they are snared with tourniquets. A venous stop-flow catheter is inserted through a prolene purse-string suture and stab incision and fed forward. The femoral artery is cannulated through a transverse incision (Fig. 24.3). Both stop-flow catheters are placed with the balloon tips at diaphragm height, and the venous catheter is placed just above the confluence of the liver veins in the vena cava (Fig. 24.4). After being correctly positioned, both catheters are again unblocked to avoid immediate, prematurely occurring hypoxia in the abdominal segment. Both thighs are blocked with pneumatic cuffs. The chemotherapeutic agents are now administered with good oxygenation as a 1–2-min bolus through the arterial line. Immediately after this both stop-flow catheters are blocked, and the extracorporeal circuit maintained for 15 min (Fig. 24.5). As chemofiltration follows immediately, leakage control in the isolated circuit proves to be unnecessary. After both stop-flow balloon catheters have been unblocked, they start the chemofiltration (Fig. 24.6) and maintain it at a maximum capacity of 500 ml per minute until at least 4 l of filtrate is substituted. In a comparative study of intra-aortic chemotherapy with versus without chemofiltration, it was shown that post-therapeutic chemofiltration lowers

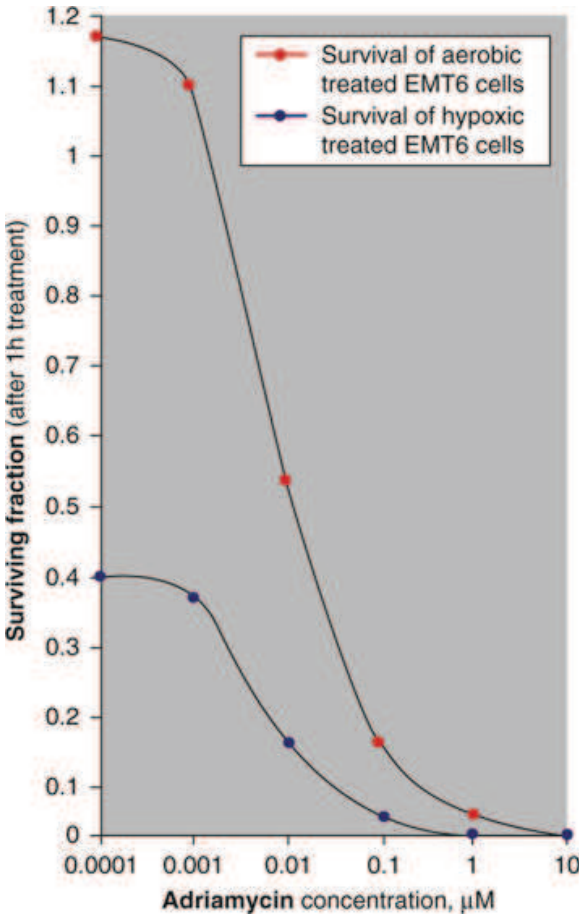

Fig. 24.2 Adriamycin toxicity to tumor cells in aerobic and hypoxic media [21]

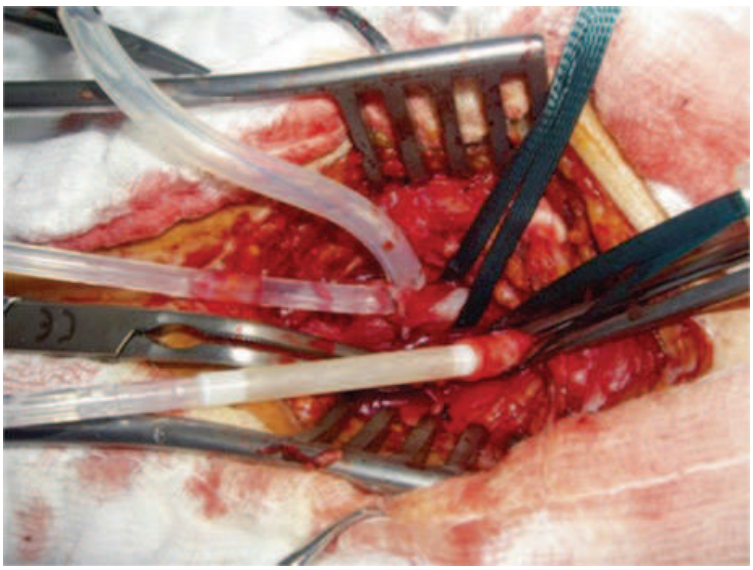

Fig. 24.3 Cannulation of the femoral vessels. The vein is cannulated by a purse-string suture, and the artery secured via a transverse incision and with a tourniquet. The arterial balloon is partially visible outside the artery in the photo. The perforations below the balloon drain the larger-diameter channel of the three lumens of the stop-flow catheter. A thinner channel is used to insufflate the balloon with a saline contrast medium mixture, and a second thin channel ends at the catheter tip and is used to feed in the guide wire to push up the catheter safely in the event of severely bent or twisted iliac arteries

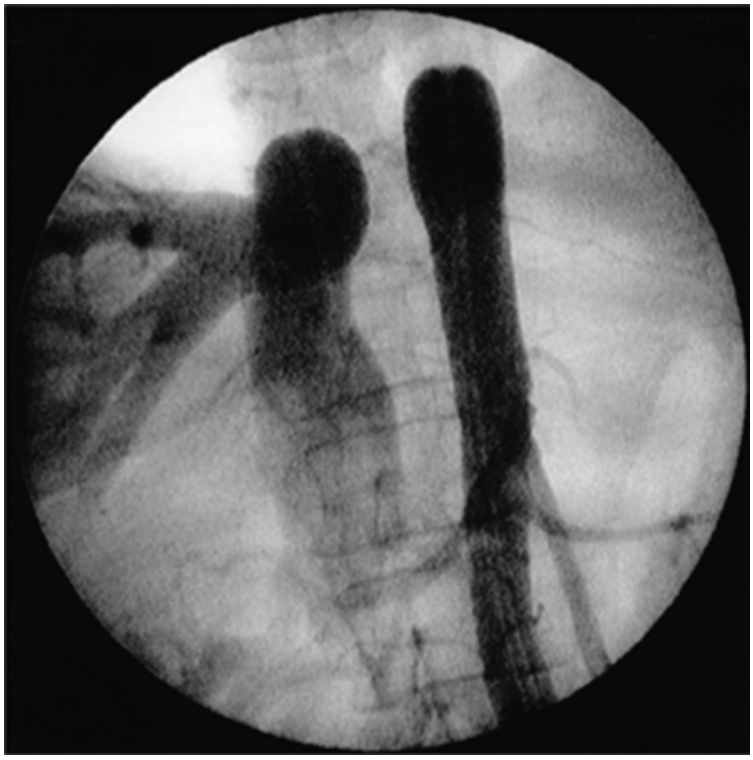

Fig. 24.4 Contrast imaging of the abdominal aorta and vena cava after contrast medium filling of both balloons with a saline contrast medium mixture and injection of contrast medium through the perforations of the stop-flow catheter's larger-diameter channel

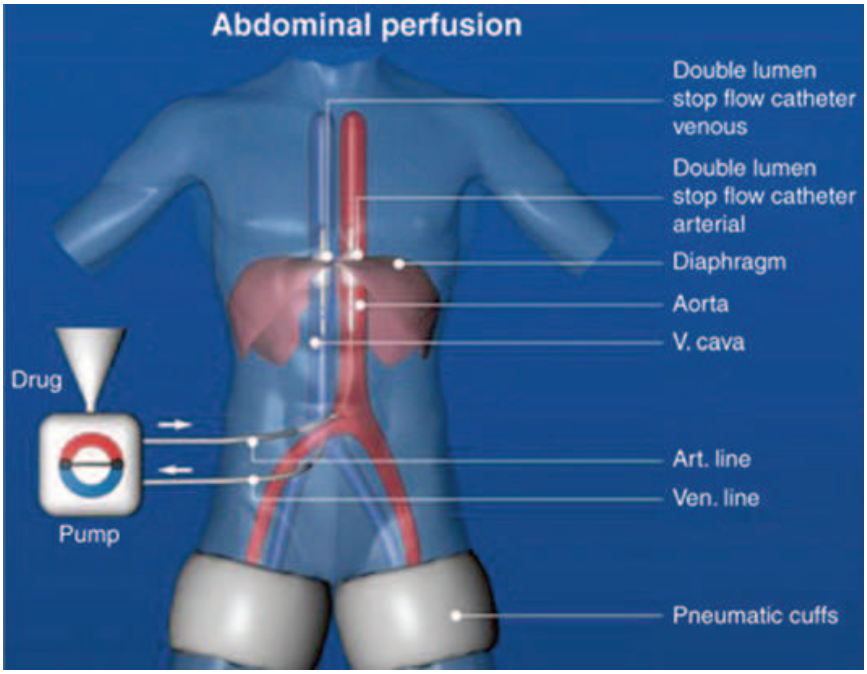

Fig. 24.5 Diagram of hypoxic abdominal perfusion. The larger-diameter channels of the aortic and venous stop-flow catheter are connected to an extracorporeal perfusion circuit. After 15 min of cytostatic exposure, the balloons are unblocked and chemofiltration begins through the same catheters

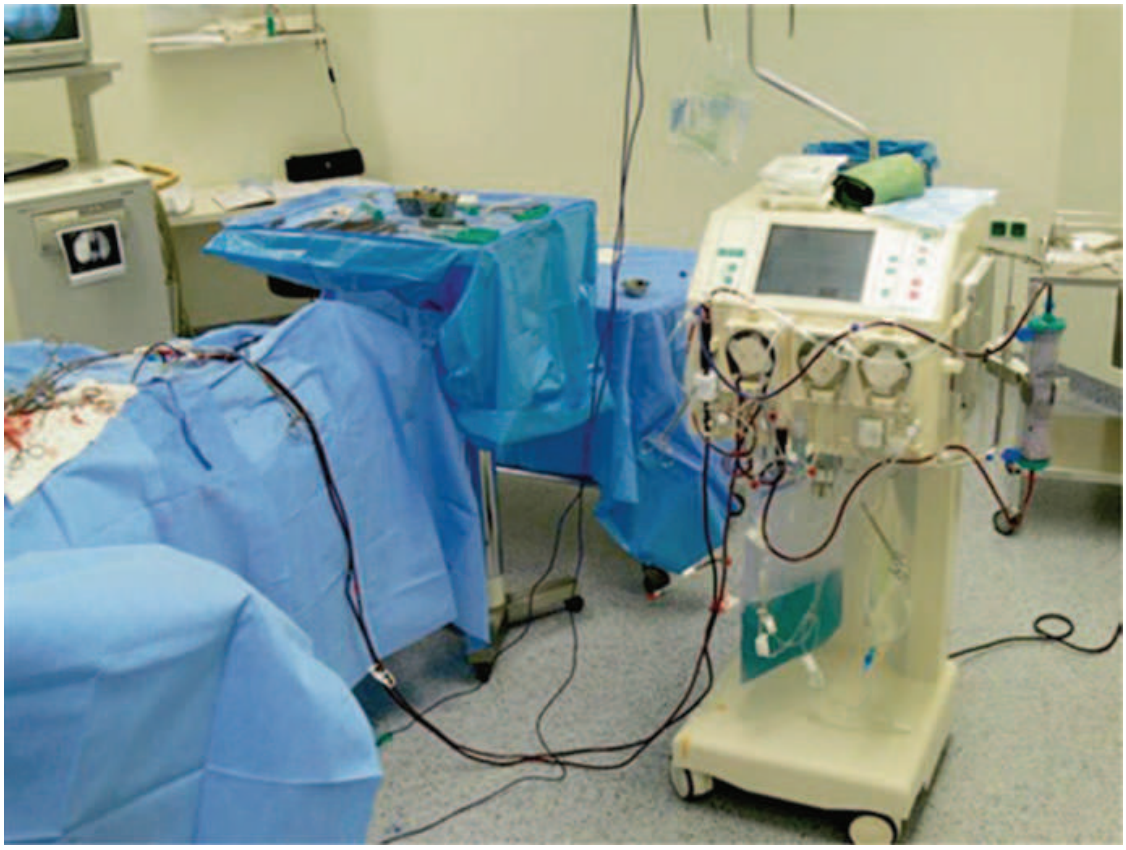

Fig. 24.6 Chemofiltration after local cytostatic exposure. The arterial and venous lines of the system are channeled out of the groin and connected to the chemoprocessor

cytostatic exposure by reducing the peak concentration so that both the immediate and subsequent cumulative toxicities are reduced, as in the case of mitomycin and adriamycin [22, 23]. After surgery and treatment, the catheters are removed and the vessels successively sutured.

24.4 Treatment Protocol

Four cycles of isolated hypoxic abdominal perfusion were conducted at 4-weekly intervals. Cisplatin, adriamycin, and mitomycin were prescribed, respectively [18]. After each treatment cycle, leukocytes and thrombocytes were monitored weekly, and monitoring occurred 2 weeks after therapy in the nadir range in 48-h intervals. The tumor marker CA 12-5 was determined immediately before each cycle and on the fifth day after, before the patient was discharged from inpatient treatment. After the second and fourth treatment session, imaging, computer tomographic monitoring was instigated.

Patients who had given their consent to it were subjected to laparotomy and explorative restaging and evaluation of their histological response rate after the final cycle. Particular importance was attached to the course of tumor marker CA 12-5 during the entire treatment, especially when a positive effect on the patient's general

Table 24.1 Patient characteristics

Stage	FIGO IIIb	4 % ($n=3$ patients)
	FIGO IIIc	71 % ($n=56$ patients)
	FIGO IV	25 % ($n=20$ patients)
Peritoneal carcinosis	4 quadrants	78 % ($n=62$ patients)
	2 quadrants	21.5 % ($n=17$ patients)
Grade of malignancy	G3	39 % ($n=31$ patients)

Table 24.2 Results

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

condition was observed due to a reduction or complete disappearance of ascites and other symptoms.

Exclusion criteria were severe comorbidities such as cardiovascular insufficiency due to coronary heart disease or absolute arrhythmia, uncontrolled diabetes, or severe infections. The leukocyte figure should not be below 2,500/µl (not with a declining trend), and the thrombocyte figure should not fall below 150,000/µl. Cytostatic agents were chosen due to the hypoxic perfusion therapy in relation to their predominant toxicity under hypoxic conditions (Figs. 24.1 and 24.2), as described by B. Teicher [21]. The overall dose of cisplatin administered via the aorta in the abdominal segment did not exceed the 70 mg limit. For adriamycin the dose limit was 50 mg, and for mitomycin 20 mg.

The patients included in this study were mainly at FIGO stage IIIc (71 %) and FIGO IV (25 %). 87.5 % had a four-quadrant peritoneal carcinosis, and interestingly 39 % ($n=31$) showed a histologic grade of G3 malignancy (Table 24.1). 79 % of all patients were heavily pretreated; six of them had already undergone third-line and one patient fourth-line therapies [18].

24.5 Results

The study endpoints were quality of life, survival time, and response rate. The clinical response rate in terms of decline of the tumor marker CA 12-5, computer tomography, and quality of life, especially in the form of reduction or complete disappearance of ascites, pain, or general discomfort, was 64 %, in comparison to 48 % histological response after an explorative second-look surgery. A complete disappearance of ascites was observed in 43 % of patients after two treatments, and

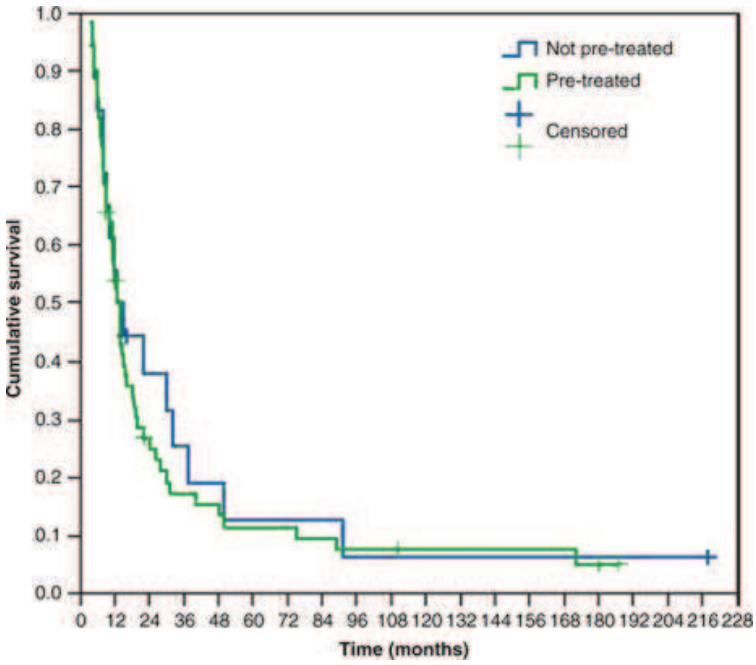

Fig. 24.7 Kaplan-Meier survival curve after hypoxic abdominal perfusion (HAP) with pretreated ($n=63$) and non-pretreated ($n=17$) FIGO III/IV ovarian cancer

a further 19 % of patients experienced a substantial decrease in abdominal fluid volume of an estimated more than 50 %. 74 % or three out of four patients reported a definite decrease in abdominal symptoms and a clear improvement in their pain situation (Table 24.2). Median progression-free survival was 8 months and median overall survival 14 months. Eight patients survived between 6 and 18 years. Of four patients who have currently survived between 11 and 19 years, three of them originally had G3 tumors. There was no statistical survival difference recorded between pretreated and non-pretreated patients (Fig. 24.7).

24.6 Toxicity

The bone marrow toxicity was not very pronounced and ranged between WHO grade 1 and 2. Only patients with previous severe third- or fourth-line chemotherapy had leukopenia and thrombocytopenia (WHO grade 3). Grade 4 toxicity or febrile neutropenia was never observed. Postoperative fatigue syndrome, whenever it occurred, was observed from the third day after surgery and was usually accompanied by post-therapeutic tumor necrosis and a temporary steep increase in LDH and CA 12-5. These syndromes are mainly observed during the first postoperative week with a focus on the second and third postoperative day, and this was the case with around 15–20 % of all patients. The predominant clinical symptom in these cases was fever and fatigue. A frequent accompanying symptom was postoperative lymphatic fistula in the groin in over 30 % of all cases. This ended without complications, however, if Redon drainage was concluded after only 14 days.

24.7 Discussion

The crucial point in treatment of ovarian cancer is that none of the cytostatic agent combinations – apart from the standard treatment with cisplatin and paclitaxel – have really produced a genuine improvement in progression-free survival (PFS), overall survival (OS), or quality of life (QoL). The limiting factor in all studies such as long-term chemotherapy, dose-intensive chemotherapy, or high-dose chemotherapy was toxicity as well as neuropathy (hand-foot syndrome), neutropenia, or fatigue and exhaustion. In addition, the lack of any formal assessment of quality of life in most studies did not allow for any conclusions about quality of life-related survival. In view of the fact that the mortality rate for ovarian cancer has hardly changed over the last 30 years, it seemed appropriate to investigate other treatment options. Based on the angiogenetic properties of ovarian cancer with extensive vascularization, the assumption was that targeted treatments that had the blood supply of neoplasia as their target would be capable of solving the problem by achieving a high tumor response rate while sparing healthy tissue at the same time. Apart from clinical effectiveness, usually in the form of prolonging progression-free survival (PFS), severe toxicity was also observed in the form of high blood pressure, bleeding, proteinuria, cardiotoxicity, and gastrointestinal toxicity with spontaneous perforations [32].

In a study of 32 patients, who had been pretreated with multiple chemotherapy regimens, positive results were observed with bevacizumab [24]. The median survival time was 6.9 months, with a median PFS of 5.5 months. These results are significantly lower compared to the isolated abdominal perfusion with a median survival time of 14 months and a PFS of 8 months. In a phase-II study to evaluate the efficacy and tolerability of bevacizumab, in patients with progressive ovarian cancer, a PFS of 4 months and an overall survival rate of 17 months were achieved. Toxicity and side effects were reported at grade 3 for hypertension and grade 4 for pulmonary embolism, vomiting, constipation, and proteinuria [25]. Even though these results appear promising, toxicity and side effects are definitely worse than after isolated perfusion and chemofiltration.

The first goal for any cancer drug or surgical treatment should be to increase the survival rate along with better quality of life. There should not actually be any other argument as the basis for recommended treatment [26]. However, thousands of patients in many studies [4–14] have been treated without any significant progress having been reported especially in relation to quality of life or survival with improved quality of life. Surgical tumor debulking and cytoreduction in advanced diseases prolong progression-free survival – but this is also limited to the early stages when what is seen as a curative operation is still possible [27].

Unfortunately, most therapeutic regimens aim for an improvement in progression-free survival (PFS) while accepting greater toxicity on the assumption that prolonged PFS will also involve prolonged overall survival. This is not always the case, however; instead prolonged overall survival is almost always associated with an extended PFS.

It is assumed that progress in the treatment of various types of cancer such as ovarian, colorectal, or testicular cancer correlates largely with the chemoresistance

of tumor stem cells. During the last three decades, the cure rates for testicular cancer have risen dramatically (from 23 % to 81 %) and those of colorectal cancer at stage 3 likewise (from 29 % to 47 %) [17], while the cure rate for ovarian cancer has hardly changed during the same period (from 12 % to 14 %). The relatively very low cure rate for ovarian cancer patients may be associated with the low response rate of epithelial ovarian cancer stem cells, where the low increase in overall survival may be a result of the reduction in the non-stem cell proportion of the tumor. This could explain why further chemotherapy can bring about renewed remission after recurrences and under some circumstances even prolong life [26]. Such a strategy could even help in exposing patients to lower levels of toxicity. The problem with chemoresistant stem cells remains, however, and these patients have only limited therapeutic options.

A basic principle to avoid systemic "drug spill" and to increase the cytostatic effect in the target area is application via the arterial blood supply of tumors, where in particular the benefit of what is called first-pass extraction, cytostatic extraction, is used in the first pass through the tumor bed, which constitutes by far the most effective part of any cytostatic treatment [28–31]. The isolated perfusion technique may result in individually adapted drug exposure (area under the AUC curve) and may break through the chemoresistance of tumor stem cells in certain cases depending on the tumor and how pronounced the chemoresistance is. This is reflected in a few long-term surviving patients after regional therapy with initially very advanced G3 tumors. Despite highly concentrated regional therapy in the abdominal segment due to simultaneous chemofiltration, they had hardly any side effects and a very good quality of life even during therapy. Thoroughgoing relief from abdominal pain and discomfort for 74 % and the complete disappearance of ascites for 43 % of patients are essential components in relation to the value of isolated perfusion therapy. With the proposed treatment objective of prolonging life with good or improved quality of life, this may be a significant advance, considering that the patients who were usually suffering from the aftereffects of previous chemotherapy and the stress of pronounced ascites at the beginning of the treatment had a life expectancy of at best 6–12 weeks at that stage. Their survival benefits after isolated regional perfusion therapy are quite obvious with this tumor activity of the peritoneal metastatic and relapsed ovarian cancer mainly restricted to the abdominal segment, as their estimated life expectancy quadrupled and patients with recurrent G3 tumors in individual cases are still surviving free of recurrence after 11–19 years. In this constellation the systemically heavily pretreated or untreatable patient, who again experiences remission after regional chemotherapy often lasting for months and years, is her own monitor. It is impossible to conduct a prospective phase-III study on systemic versus regional chemotherapy with systemically untreatable patients, who still suffer from the aftereffects of toxicity, as their bone marrow reserves are often exhausted, the patients are considered untreatable, and they normally refuse further therapy.

The quality of life in cancer treatment is a parameter which should be focused on primarily, especially as newer treatment options only result in only minimal extensions of PFS or overall survival – 1, 2, or 3 months, if at all – and this at the expense

of quite considerable toxicity and even a huge increase in the financial burden [33]. In this respect, a phase-III study, which investigates regional versus systemic chemotherapy among previously untreated patients, will be very important and could provide information about therapeutic options to be adopted in the future.

References

1. Gore ME, Fryatt I, Wiltshaw E, Dawson T. Treatment of relapsed carcinoma of the ovary with cisplatin or carboplatin following initial treatment with these compounds. Gynecol Oncol. 1990;36:207–11.
2. Markman M, Rothman R, Hakes T, et al. Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatin. J Clin Oncol. 1991;9:389–93.
3. Ozols RF. Treatment of recurrent ovarian cancer: increasing options – "recurrent" results. J Clin Oncol. 1997;15:2177–80.
4. Dark GG, Calvert AH, Grimshaw R, Poole C, Swenerton K, Kaye S, et al. Randomized trial of two intravenous schedules of the topoisomerase I inhibitor liposomal lurtotecan in women with relapsed epithelial ovarian cancer: a trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 2005;23:1859–66.
5. Gore M, Mainwaring P, A'Hern R, et al. Randomized trial of dose-intensity with single-agent carboplatin in patients with epithelial ovarian cancer. London Gynaecological Oncology Group. J Clin Oncol. 1998;16:2426–34.
6. Jodrell DI, Egorin MJ, Canetta RM, Langenberg P, Goldbloom EP, Burroughs JN, et al. Relationships between carboplatin exposure and tumor response and toxicity in patients with ovarian cancer. J Clin Oncol. 1992;10:520–8.
7. Levin L, Hryniuk WM. Dose intensity analysis of chemotherapy regimens in ovarian carcinoma. J Clin Oncol. 1987;5:756–67.
8. McGuire WP, Hoskins WJ, Brady MF, et al. Assessment of dose-intensive therapy in suboptimally ovarian cancer: a Gynecologic Oncology Group study. J Clin Oncol. 1995;13:1589–99.
9. Omura GA, Brady MF, Look KY, Averette HE, Delmore JE, Long HJ, et al. Phase III trial of paclitaxel at two dose levels, the higher dose accompanied by filgrastim at two dose levels in platinum-pretreated epithelial ovarian cancer: an intergroup study. J Clin Oncol. 2003;21:2843–8.
10. Thigpen JT. Dose-intensity in ovarian carcinoma: hold, enough? J Clin Oncol. 1997;15:1291–3.
11. Grenman S, Wiklund T, Jalkanen J, et al. A randomised phase III study comparing high-dose chemotherapy to conventionally dosed chemotherapy for stage III ovarian cancer: the Finnish Ovarian (FINOVA) study. Eur J Cancer. 2006;42:2196–9.
12. Möbus V, Wandt H, Frickhofen N, Bengala C, Champion K, Kimming R, et al. Phase III trial of high-dose sequential chemotherapy with peripheral blood stem cell support compared with standard dose chemotherapy for first-line treatment of advanced ovarian cancer: intergroup trial of the AGO-Ovar/AIO and EBMT. J Clin Oncol. 2007;25:4187–93.
13. du Bois A, Weber B, Rochon J, et al. Addition of epirubicin as a third drug to Carboplatin-paclitaxel in first-line treatment of advanced ovarian cancer: a prospectively randomized gynecologic cancer intergroup trial by the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group and the Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens. J Clin Oncol. 2006;24:1127–35.
14. Fung MF, Johnston ME, Eisenhauer EA, Elit L, Hirte HW, Rosen B, et al. Chemotherapy for recurrent epithelial ovarian cancer previously treated with platinum – a systematic review of the evidence from randomized trials. Eur J Gynaecol Oncol. 2002;23:104–10.
15. Markman M, Liu PY, Moon J, et al. Impact on survival of 12 versus 3 monthly cycles of paclitaxel (175 mg/m^2) administered to patients with advanced ovarian cancer who attained a

complete response to primary platinum-paclitaxel: follow-up of a Southwest Oncology Group and Gynecologic Oncology Group phase 3 trial. Gynecol Oncol. 2009;114:195–8.
16. Markman M, Liu PY, Wilczynski S, et al. Phase III randomized trial of 12 versus 3 months of maintenance paclitaxel in patients with advanced ovarian cancer after complete response to platinum and paclitaxel-based chemotherapy: a Southwest Oncology Group and Gynecologic Oncology Group trial. J Clin Oncol. 2003;21:2460–5.
17. Huang L, Cronin Kathleen A, Johnson Karen A, Mariotto Angela B, Feuer Eric J. Improved survival time: what can survival cure models tell us about population-based survival improvements in late-stage colorectal, ovarian, and testicular cancer? Cancer. 2010;112:2289–300.
18. Aigner KR, Gailhofer S, et al. Hypoxic abdominal perfusion for recurrent platinum refractory ovarian cancer. Cancer Ther. 2008;6:213–20.
19. Creech O, Krementz ET, Ryan RF, Winbald JN. Chemotherapy of cancer: regional perfusion utilizing an extracorporeal circuit. Ann Surg. 1958;148:616–32.
20. Kroon BBR. Regional isolated perfusion in melanoma of the limbs; accomplishments, unsolved problems, future. Eur J Surg Oncol. 1988;14:101–10.
21. Teicher BA, Lazo JS, Sartorelli A. Classification of antineoplastic agents by their selective toxicities toward oxygenated and hypoxic tumor cells. Cancer Res. 1981;41:73–81.
22. Aigner KR, Gailhofer S. High dose MMC: aortic stopflow infusion (ASI) with versus without chemofiltration: a comparison of toxic side effects (abstract). Reg Cancer Treat. 1993;6 Suppl 1:3.
23. Muchmore JH, Aigner KR, Beg MH. Regional chemotherapy for advanced intraabdominal and pelvic cancer. In: Cohen AM, Winawer SJ, Friedman MA, Gunderson LL, editors. Cancer of the colon, rectum and anus. New York: McGraw Hill; 1995. p. 881–9. In Albert Cohn Colorectal Cancer.
24. Monk BJ, Han E, Joseph-Cowen CA, Pugmire G, Burger RA. Salvage bevacizumab (rhuMAB VEGF)-based therapy after multiple prior cytotoxic regimens in advanced refractory epithelial ovarian cancer. Gynecol Oncol. 2006;102:140–4.
25. Burger RA, Sill MW, Monk BJ, Greer BE, Sorosky JI. Phase II trial of Bevacizumab in persistent or recurrent epithelial ovarian cancer of primary peritoneal cancer: a Gynecologic Oncology Group Study. J Clin Oncol. 2007;25:5165–71.
26. Cannistra SA. The ethics of early stopping rules: who is protecting whom? J Clin Oncol. 2004;22:1542–5.
27. Crawford SC, Vasey PA, Paul J, Hay A, Davis JA, Kaye SB. Does aggressive surgery only benefit patients with less advanced ovarian cancer? Results from an international comparison within the SCOTROC-1 trial. J Clin Oncol. 2005;23:8802–11.
28. Stephens FO, Harker GJS, Crea P. The intra-arterial Infusion of chemotherapeutic agents as “basal” treatment of cancer: evidence of increased drug activity in regionally infused tissues. Aust N Z J Surg. 1980;50:597–602.
29. Stephens FO. Why use regional chemotherapy? Principles and pharmacokinetics. Reg Cancer Treat. 1988;1:4–10.
30. Stephens FO. Induction (neo-adjuvant) chemotherapy systemic and arterial delivery techniques and their clinical applications. Aust N Z J Surg. 1995;65:699–707.
31. Stephens FO. Induction (neo-adjuvant) chemotherapy: the place and techniques of using chemotherapy to downgrade aggressive or advanced localised cancers to make them potentially more curable by surgery and/or radiotherapy. Eur J Surg Oncol. 2001;27(7):627–88.
32. Stone Rebecca L, Sood Anil K, Coleman RL. Collateral damage: toxic effects of targeted antiangiogenic therapies in ovarian cancer. Lancet Oncol. 2010;11:465–75.
33. Aigner KR, Stephens FO. Guidelines and evidence-based medicine – evidence of what? EJCMO 2012. Published online. http://www.slm-oncology.com/Guidelines_and_Evidence_Based_Medicine_Evidence_of_What_,1,272.html.