Int. J. Hyperthermia, March 2010; 26(2): 118–126

informa
healthcare

RESEARCH ARTICLE

Regional abdominal hyperthermia combined with systemic chemotherapy for the treatment of patients with ovarian cancer relapse: Results of a pilot study

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(Received 24 May 2009; Revised 27 September 2009; Accepted 28 September 2009)

Abstract

Purpose: Due to the poor prognosis of patients with ovarian cancer relapse (OCR), newer strategies are warranted to improve the therapeutic index. We performed a prospective phase I/II-study of regional abdominal hyperthermia (RHT) combined with systemic chemotherapy in OCR patients in order to evaluate outcome, efficacy and tolerance.

Materials and methods: OCR patients with an Eastern Cooperative Oncology Group status <2, without any thromboembolic disease or severe cardiovascular co-morbidities, and pre-treated with at least one systemic chemotherapy regimen due to epithelial ovarian cancer were enrolled into the present study. RHT was applied using a SIGMA 60 applicator and a Hybrid-System SIGMA-Eye/MRT composed of a 1.5T-MRT and a Sigma-Eye-applicator.

Results: Overall, 36 OCR patients were enrolled. The majority of the patients (>80%) were classified as platinum resistant. The most common chemotherapeutic agent applied was pegylated-liposomal-doxorubicin (47.2%) followed by carboplatin (16.6%) and topotecan (13.9%). One patient (2.8%) achieved a complete remission (CR), 12 patients (33.3%) yielded a partial remission (PR) and 16 patients (44.4%) developed a progressive disease (PD). In platinum-sensitive patients we observed higher response (57.1% versus 31%) and lower progression rates (28.6% versus 48.3%) than in platinum-resistant patients. Eleven patients (30.5%) discontinued treatment due to toxicity. The main toxicity was a haematological one with grade 3/4 anaemia, leucopenia and thrombocytopenia occurring in 13.9%, 5.6% and 8.3%, respectively. Median overall survival was 12 months (range: 1–48), while median progression-free survival was 5 months (range: 0.5–34).

Conclusions: Our results demonstrate the feasibility of RHT combined with systemic treatment. Prospective phase III trials are warranted to evaluate the benefit and efficacy in heavily pre-treated patients with OCR.

Keywords: *regional-abdominal hyperthermia, chemotherapy, ovarian cancer relapse, toxicity, platinum resistance*

Introduction

Hyperthermia therapy, during which body tissue is exposed to high temperatures, has the effect of killing or weakening tumour cells by a concurrent limited effect on healthy cells. Tumour cells, with a disorganized and compact vascular structure, have difficulty dissipating heat. Hyperthermia may therefore cause their apoptosis by denaturation and coagulation of regulatory cellular proteins [1–3]. Even if hyperthermia does not induce apoptosis of cancer cells, they may become more susceptible to certain chemotherapeutic agents, thereby increasing their therapeutic index. Former preclinical *in vitro* studies in various experimental settings were able to indicate that hyperthermia would enhance the cytotoxic effects of carboplatin, thus overcoming any drug resistance acquired [4–6].

In an attempt to improve the unfavourable clinical outcome of relapsed ovarian cancer, hyperthermia has been applied in experimental settings for

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ISSN 0265–6736 print/ISSN 1464–5157 online
DOI: 10.3109/02656730903369200

advanced stages of the disease with concomitant systemic chemotherapy. The applied chemotherapeutic agents were mainly platinum-based, such as cisplatin or carboplatin [7–13]. Consistent with the preclinical models, most study results suggest that hyperthermia may overcome platinum resistance in advanced ovarian cancer, although there is still no consistent evidence that hyperthermia contributes to any clinical improvement beyond chemotherapy alone [11]. Furthermore, many authors report a significant dose-limiting, mainly due to haematological toxicities [11, 13, 14].

The primary aim of the present feasibility study was to evaluate the efficacy, feasibility and tolerance of regional abdominal hyperthermia in conjunction with platinum- and non-platinum-based agents in patients with platinum-resistant or platinum-sensitive ovarian cancer relapse. Despite the fact that no conclusive *in vitro* data exist which prove the enhancement of the efficacy of non-platinum agents such as pegylated liposomal doxorubicin or topotecan in combination with hyperthermia, in this pilot study we wanted to demonstrate that hyperthermia can also be safely combined with non-platinum cytotoxic agents applied in platinum resistant and heavily pre-treated patients with ovarian cancer. Various pre-clinical and early phase I studies indicate promising activity and show encouraging results of topotecan or pegylated liposomal doxorubicin in combination with hyperthermia in different solid tumours [28–32].

Our results will constitute the basis of future phase III trials as a possibility to establish the inclusion of hyperthermia as an adjunct to palliative chemotherapy in ovarian cancer patients.

Materials and methods

Study design

The present study was a pilot study with the primary end-point: feasibility of hyperthermia combined with systemic chemotherapy measured by the induced toxicity. The secondary end point was to describe the potential efficacy of the combined treatment defined by specific response criteria, cancer-related death and progression of the disease. All 36 patients were evaluated according to the intention to treat analyses (ITT) for both phase I (feasibility) and II (efficacy) objectives of the study. The initially planned number of patients was 40. All data were assessed in a prospective way. No dose increasing strategy in the phase I part of the study was followed.

The quality of hyperthermia was measured by the maximal total power achieved by the applicator used, as well as the maximum temperatures achieved in 179 heating sessions as measured vaginally and/or sublingually.

Patient selection

Thirty-six patients with relapse of epithelial ovarian cancer were recruited into the present study over a 5-year period (2002–2007). Patients were eligible if they had an Eastern Cooperative Oncology Group (ECOG) performance status [15] of 0 or 1, an age above 18 years, no severe co-morbidities, no second malignancies, creatinine clearance $\geq$30 mL/min, adequate bone marrow function defined as white blood cell count (WBC) >1000/mL cells, and an absolute granulocyte count of $\geq 1.5 \times 10^9$/L cells and a platelet count of $\geq 100 \times 10^9$/L. All patients had at least one prior systemic chemotherapy pre-treatment due to ovarian cancer in their medical history. Exclusion criteria were any thromboembolic disease, central nervous system metastases, respiratory insufficiency, congestive heart failure and severe cardiovascular impairment. Patients were selected from the overall population of ovarian cancer of our hospital if they were in a good performance status (ECOG $\leq$1), had a good compliance, and mainly wished to be treated in a hyperthermic regime. Yearly we systemically treat approximately 100–120 patients. Another relevant point is that since we are a centre for clinical studies, the vast majority of our patients were enrolled in various other chemotherapy studies.

The study was approved by the Research Ethics Committee of the Charité (Application and Decision No. EA2/061/07). Participants gave their written informed consent before entering the study.

Patients were classified by platinum-resistant versus platinum-sensitive disease. Platinum resistance was defined either as a recurrence during six months after previous platinum-based chemotherapy or as a progression during a platinum-based regime [8]. Patients were treated by various chemotherapeutic agents determined by the treating gynaecological oncologist in an interdisciplinary tumour board according to the current guidelines of the Ovarian Cancer Study Group (Arbeitsgemeinschaft Gynaekologische Onkologie, AGO-Ovar), as based on the pre-treatment regimes of the patients, their platinum-sensitivity status and their co-morbidities [27]. The cytotoxic substances applied were pegylated liposomal doxorubicin, treosulfan, docetaxel, topotecan and carboplatin – as a monotherapy or in combination with gemcitabine. Details are presented in Table I.

RHT and supportive care

RHT was added to the systemic chemotherapy. The hyperthermia schedule was adapted according to each chemotherapy application regimen. The therapy

Table I. Cancer- and therapy-related characteristics of the 36 patients with ovarian cancer relapse after chemotherapy combined with regional abdominal hyperthermia.

	All patients ($n = 36$)
Mean age (years)	53.32 ± 9.86
# patients >60 years	10 (27.8%)
Initial FIGO-Stage	
I/II	1 (2.8%)
III	29 (80.5%)
IV	6 (16.7%)
Distant metastases	20 (55.5%)
Liver	13 (36.1%)
Pleura	6 (16.7%)
Abdominal wall	4 (11.1%)
Chemotherapy line	
Second	4 (11.1%)
Third	17 (47.2%)
Fourth	10 (27.8%)
Fifth	3 (8.3%)
Sixth	2 (5.6%)
Chemotherapeutic agent	
Pegylated liposomal doxorubicin	17 (47.2%)
Topotecane	5 (13.9%)
Treosulfan	2 (5.6%)
Paclitaxel/docetaxel	2 (5.6%)
Gemcitabine	2 (5.6%)
Cyclophosphamide	1 (2.8%)
Carboplatin, mono	1 (8.3%)
Carboplatinum-based combination	3 (8.3%)
Platinum sensitive	7 (19.4%)
Platinum resistant	29 (80.6%)

was applied in a hospital setting (non-ambulatory). All patients were usually observed for at least 24 h after treatment before they were discharged. No routine application of the granulocyte colony stimulating factor (G-CSF) or of erythropoietin were allowed.

To apply RHT, a Sigma-60 (S-60) applicator with four antenna pairs and a sigma-Eye/MR (S-Eye/MR) applicator with 12 antenna pairs were used. The S-Eye/MR applicator is tuned in such a way as to be compatible with an MR-tomograph (Siemens Symphony 1.5,Tesla, Germany). A length of 4 cm was required as the minimum water distance between the antennae and the body surface. The RHT was performed according to a standard protocol. The applicator's mid plane was positioned on the patient's navel for abdominal heating. An optimum of 30 min was required to achieve a steady-state temperature of 41–42°C in a reference point under ideal conditions. The steady-state time (therapeutic time) was assessed after 60 min. A therapeutic time below 30 min was defined as a disrupted treatment.

Power and temperature data were acquired for the S-60 and S-Eye/MR. Temperature–time curves were registered for each patient in one reference point either via the vagina (orifice or stump after hysterectomy), in the rectum or in the anus praeter as well as sublingually (orally) in order to estimate the systemic temperature.

A limiting parameter of the treatment was a heat intolerance or haematological toxicity as described below. In cases of some intolerance or side effects induced by the heat, but without early termination of the therapy, the physician in charge was usually able to address the problem by reducing the total power, changing the phases of the channels, repositioning the patient, cooling the bolus water, using water bags, or administering medication – especially in the case of edge effects.

Toxicity evaluation

Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (CTC; version 2.0) [15, 16]. Dose modifications (25% dose reduction of chemotherapy) were applied in the case of increased renal retention values during therapy (creatinine clearance <60 mL/min). In cases of febrile neutropenia or thrombocytopenia $<100 \times 10^9$/L, treatment had to be delayed until the recovery of marrow function had been ascertained.

Response evaluation

Responses were classified according to Response Evaluation Criteria In Solid Tumors (RECIST) criteria [17]. CT scans of measurable and assessable sites were carried out within 4 weeks before the start of the treatment and repeated every 3 cycles or when clinically indicated. Responses were confirmed by CT scan approximately 4 weeks after determining the initial response. Measurement for CA 125 was performed in addition, to evaluate the response to therapy. The time to progression was measured from the start of the treatment until progression. Overall survival was defined as being the time between the start of the treatment and that of death or the last follow-up date. A follow-up of the patients after completion of treatment took place every 3 months via clinical examination, tumour marker values CA125, and transabdominal/transvaginal sonography. A CT or MRI scan was then performed in those cases where a tumour relapse had been suspected. Relapse was then defined according to the RECIST criteria [17].

Statistical analysis

Analyses were conducted in an exploratory fashion. All results are presented in raw numbers, rates, or medians and ranges, mean ± standard deviation according to the underlying distribution. Binomial-exact 95%-confidence intervals (CI) are also reported. The analyses of time-to-event data in the case of recurrence and overall survival were

calculated according to the Kaplan-Meier method and survival curves were compared using the log-rank test. For the calculation of recurrence-free and overall survival, the interval between start of chemotherapy and date of tumour progression, death or last contact was analysed. Statistical analyses were performed by SPSS 15 (SPSS, Chicago) and GraphPad Prism 5 statistical software® (GraphPad, La Jolla, CA).

Results

Response and survival

Overall, 36 patients with ovarian cancer relapse under palliative systemic chemotherapy combined with RHT were evaluated. All patients were assessable for the safety analysis and evaluable for response. The mean patient age was 53.32 years ± 9.8 (SD); (range: 25–68). The mean follow-up period was 12.9 ± 12.63 SD months (range: 1–48 months). Seven patients (19.4%) were platinum sensitive, while 29 patients (80.6%) were platinum resistant. Overall, 20 patients (55.5%) had distant metastases in liver parenchyma (36.1%), pleura (16.7%) and abdominal wall (11.1%). The majority of the patients (47.2%) was under third-line chemotherapy and the most common chemotherapeutic agent applied was pegylated liposomal doxorubicin (47.2%) followed by topotecan in 13.9% of the patients. The initial Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) stage of the majority of the patients (80.5%) was stage III. Detailed cancer-related patient characteristics are presented in Table I. The median overall survival (OS) was 12 months (range: 1–48; 95%CI: 9.8–14.19), while the median progression-free survival (PFS) was 4 months (range: 0.5–34; 95%CI: 2.17–5.82). The Kaplan-Meier survival curves of OS and PFS are presented in Figure 1. Only one patient showed a complete response to treatment and still continues RHT and pegylated liposomal doxorubicin over a period of 2.5 years every 4 weeks; within the last year, bevacizumab has been added. This patient was 22 years old, with a heavily pre-treated platinum resistant relapsed ovarian cancer. The combination of pegylated doxorubicin and hyperthermia achieved a complete response. However, due to the high risk of tumour progression the patient desired the addition of bevacizumab. Until now, we have not observed additional side effects. Last examination in June 2009 confirmed no evidence of disease.

During the follow-up period, 22 (61.1%) of the 36 patients died and all patients (97.2%) but one experienced a new relapse or progression of the malignant disease. Sixteen patients (44.4%) presented a rapid progressive disease still being under

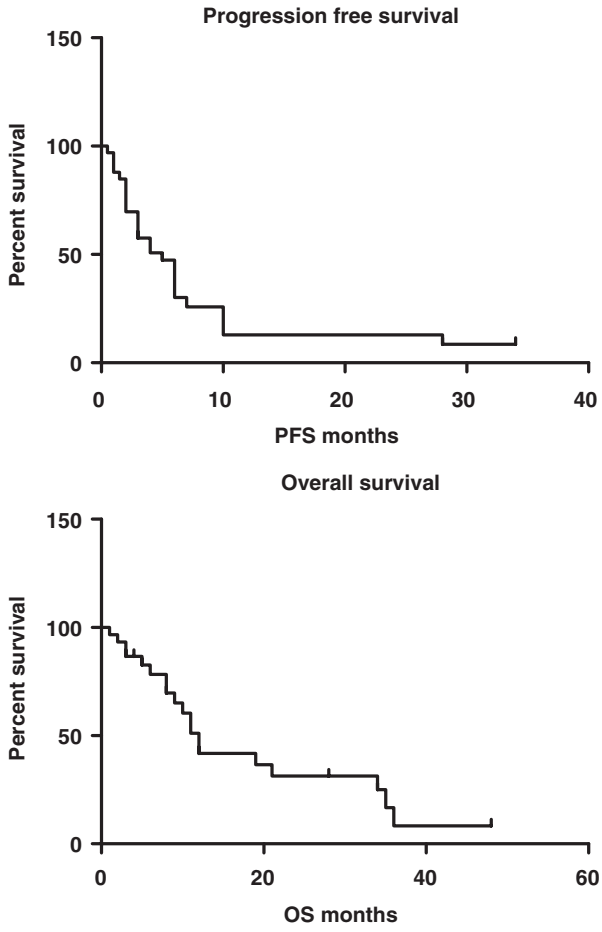

Figure 1. Kaplan-Meier survival curves and data for overall and progression-free survival for the 36 patients with ovarian cancer relapse after chemotherapy combined with regional abdominal hyperthermia. Point 0, beginning of combination treatment; PFS, progression-free survival; OS, overall survival.

combined treatment, which also led to discontinuation of treatment. Twelve patients (33.3%) presented a partial response according to imaging studies (CT or MRI). When dividing the patients into platinum resistant and platinum sensitive, we see that the latter had higher rates of overall response (31% versus 57.1%) and lower rates of rapid progressive disease under treatment (48.3% versus 28.6%).

The median OS separately for platinum-sensitive and platinum-resistant patients was 12 months (95%CI: 4.53–19.46) and 12 months (95%CI: 3.32–20.67), respectively and so not significantly different ($p = 0.86$). The median PFS for platinum-sensitive and platinum-resistant patients was 6 months (95%CI: 2.54–7.26) and 3 months (95%CI: 1.38–4.62), respectively. These PFS values were also not significantly different ($p = 0.57$) between the two groups. The fact that no statistical significance could be reached between the two groups is probably attributable to the small number of

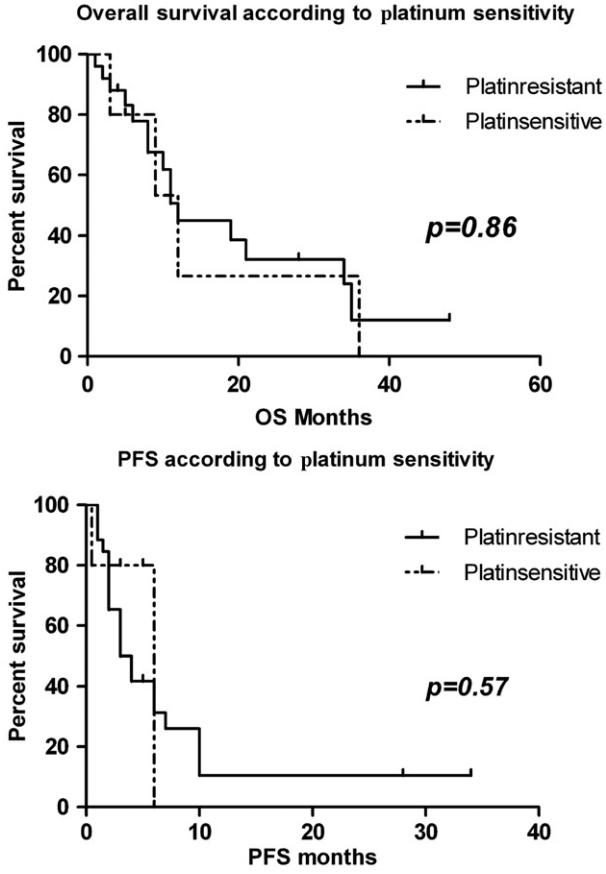

Figure 2. Kaplan-Meier curves of describing overall and progression-free survival for platinum-sensitive ($n = 7$) and platinum-resistant ($n = 29$) patients. Point 0, beginning of hyperthermia treatment; PFS, progression-free survival; OS, overall survival.

patients; especially the platinum-sensitive ones. The equivalent Kaplan-Meyer survival curves for platinum-resistant and -sensitive patients are presented in Figure 2.

Course of therapy and toxicity

Thirty-six patients received a total of 179 RHT treatment cycles. The median number of applied treatment cycles per patient was 4 (range: 1–22) and the average number per patient was 5.1 ± 4 (SD). Only 6 (16.7%) of the 36 patients completed all initially scheduled cycles of chemotherapy combined with RHT. In 11 patients (30.5%) treatment had to be discontinued due to haematological toxicity (10.3%), gastrointestinal symptoms such as severe nausea, vomiting or diarrhoea (3.4%), allergy or cutaneous exanthema (6.8%), and acute renal failure in one patient. One further patient discontinued therapy due to personal reasons. In all other patients, therapy was stopped due to rapid progressive disease with clinical symptoms such as mechanical ileus and ascites. In 10 patients (27.8%), isolated treatment cycles had to be delayed for 1 to 2 weeks on average due to thrombocytopenia or a reduced general condition of the patients. The reported toxicity was related to both RHT and systemic chemotherapy. Data are presented in Table II.

The overwhelming majority of the heating sessions took 30 to 60 min to complete; generally they lasted for approximately 60 min (time at steady state temperature plateau). The mean maximum total power (W) achieved by the applicator, was 646.6 ± 70.58 W (range: 450–720; 95%CI: 615.6–665.6).

The values of the maximum temperatures achieved in 179 heating sessions were as follows: mean temperature as measured in the rectum or in the anus praeter was $41.72 \pm 0.26^{\circ}$C (range: 41.3–42.1; 95%CI: 41.6–41.83). The mean maximum temperature sublingually was $37.4 \pm 0.17^{\circ}$C.

We found no evidence for heat-specific acute, sub acute or chronic toxicities such as thermal burns or tissue damage. When evaluating the parameters TRISE(vaginal) and TRISE (rectal) according to Franckena et al. [33], we measured on average values of 2.72 and 2.84 respectively. In a univariate analysis, TRISE was significant for the response rate ($p = 0.03$), though a multivariate analysis was not representative due to the small number of patients. Also significant for the response rate were platinum sensitivity and the absence of distant metastases ($p < 0.01$). TRISE was measured according to the formula:

$$\mathrm{TRISE} = \frac{\sum_{n=1}^{n=\max} (\mathrm{ALT50} - 37^{\circ}\mathrm{C}) \times \mathrm{d}t}{450}$$

The toxicity profile of the combined treatment classified into CTC grade 1 to 2 and grade 3 to 4 is presented in detail in Table III. Although a mild (grade 1 to 2) anaemia, thrombocytopenia and leucopenia was developed by 30.5%, 22.2% and 38.9% of the patients respectively, only 13.9%, 8.3% and 5.6% of the patients developed severe, grade 3 to 4, haematological disturbances. Other side effects such as nausea and vomiting, electrolyte disturbances and allergic reactions occurred in the majority of the cases to only a rather mild degree. In one patient severe hyponatraemia of 125 mmol/L occurred during the third treatment cycle and resulted in impaired consciousness.

Discussion

Over the last 25 years, five-year survival rates for patients with advanced epithelial ovarian cancer have improved from 36% in the mid 1970s to 45% by the year 2002 [18]. However, since approximately 75% of women with epithelial ovarian cancer initially

Table II. Clinical course and response to therapy of the 36 patients with ovarian cancer relapse under chemotherapy combined with RHT.

Therapy: systemic chemotherapy + RHT	Platinum-sensitive patients ($n = 7$)	Platinum-resistant patients ($n = 29$)	All patients ($n = 36$)
Complete response	0	1 (3.4%)*	1 (2.8%)
Progressive disease	2 (28.6%)	14 (48.3%)	16 (44.4%)
Partial response	4 (57.1%)	8 (27.6%)	12 (33.3%)
Early end of therapy due to side effects:	3 (42.8%)	8 (27.6%)	11 (30.5%)
GI-toxicity	1 (14.3%)	1 (3.4%)	2 (5.6%)
Haematological toxicity	1 (14.3%)	3 (10.3%)	4 (11.1%)
Poor general condition	1 (14.3%)	2 (6.8%)	3 (8.3%)
Allergy or cutaneous reaction		2 (6.8%)	2 (5.6%)
Renal failure		1 (3.4%)	1 (2.8%)

*One platinum-resistant patient still continues therapy upon complete response.

Table III. Common and RHT-related toxicity.

$N = 36$	Grade 1 to 2	Grade 3 to 4
Anaemia	11 (30.5%)	5 (13.9%)
Thrombopenia	8 (22.2%)	3 (8.3%)
Leucopenia	14 (38.9%)	2 (5.6%)
Nausea/vomiting	7 (19.4%)	1 (2.8%)
Diarrhoea	5 (13.9%)	1 (2.8%)
Renal failure	3 (8.3%)	1 (2.8%)
Dyspnoea	–	1 (2.8%)
Cutaneous reaction	1 (2.8%)	1 (2.8%)
Hyponatraemia	–	1 (2.8%)
Hypokalaemia	15 (41.7%)	2 (5.6%)

present with stage III or IV disease the vast majority of the patients (60–85%) will suffer from a tumour relapse [19]. The selection of salvage therapy is commonly based upon whether women are 'sensitive' or 'resistant' to initial platinum-based treatment. Patients who respond to initial platinum-based therapy and have a significant relapse-free interval (more than six months) have a high probability of responding again to platinum-based treatment at the time of relapse. The length of the prior response is highly predictive of the upper limit of the duration of disease control that can be expected with second-line platinum-based chemotherapy [21]. The length of the treatment-free interval is an important predictor of outcome. This was illustrated in a report that included 72 patients with measurable disease recurrence who had received at least two platinum-based regimens, and who had a treatment-free interval of at least four months. Treatment outcome was stratified according to the length of the treatment-free interval: With a treatment-free interval between 5 and 12 months, the response rate was 27%, and the pathological CR rate was 5%. With a treatment-free interval of 13 to 24 months, the response rate was 33%, and the pathological CR rate was 11%. With a treatment-free interval of longer than 24 months, the response rate was 59% and the pathological CR rate was 22% [22].

Successful management of women who are platinum resistant requires the use of non-cross-resistant agents. Single agent therapy is usually chosen, since combination regimens are more toxic, but without a proven survival benefit compared to single agent therapy. Many cytotoxic agents are considered to be active, including paclitaxel, docetaxel, cyclophosphamid, pegylated liposomal doxorubicin, topotecan, gemcitabine, vinorelbine and treosulfan. The overall response rates vary between 25% for paclitaxel weekly [23], 17% for pegylated liposomal doxorubicin [24], 15% for topotecan [25] and 13–21% for gemcitabine [26]. Toxicity profiles also vary with a myelotoxicity profile (grade 3 or 4 neutropenia) as high as 12% for liposomal doxorubicin and 8% febrile neutropenia for topotecan.

In the present study we treated 29 platinum-resistant patients and 7 platinum-sensitive patients with recurrent epithelial ovarian carcinoma with systemic chemotherapy in combination with RHT. The thermal enhancement of platinum drugs is well established [4–6], but since we also applied non-platinum agents in platinum resistant patients, we aimed to demonstrate the feasibility and efficacy of non-platinum agents in combination with hyperthermia.

We report high rates of progressive disease; all patients but one experienced a new relapse during the follow-up period with a mean time to progression of 8.62 months. This may be attributed to the fact that the majority of our patients were heavily pretreated in a highly palliative situation and had already suffered from two or three recurrences of the malignant disease. However, despite the previous polychemotherapy regimes of most of our patients, we do report acceptable overall toxicity rates of the combined treatment. Severe episodes of haematological toxicity that led to discontinuation of therapy constituted only 11%. We report no severe

incidences of cardiovascular complications during treatment, which may be accredited to the fact that patients with serious cardiovascular co-morbidity were precluded from the study.

Even if 30.5% of the patients discontinued the treatment due to toxicity (11% due to haematological toxicity), one has to consider that our patient collective was mainly platinum resistant and thus in a highly palliative situation, with 75% of the patients being already in the third or fourth chemotherapy line. These patients were heavily pre-treated and therefore had limited therapeutic reserves. When comparing our results to the toxicity profile of pegylated liposomal doxorubicin alone, no unusual higher toxicity rates are noticed. In a recent review by Strother et al. about pegylated liposomal doxorubicin in ovarian cancer [34], considerable grade 3-4 hematologic toxicity (mainly neutropenia), ranges from 12% to 46%.

In a comparable study by Cho et al. on 45 patients with peritoneal carcinomatosis treated with systemic chemotherapy and RHT, the authors found no evidence of heat-specific subacute or chronic toxicities such as thermal burns or tissue damage [12]. Furthermore, we can confirm their conclusion that the observed toxicities with RHT are comparable to known side effects of chemotherapy without hyperthermia. In contrast to our results, Atmaca et al. report in a recently published evaluation of 47 patients with whole body hyperthermia an overall cardiac toxicity rate of 49% (47% of mild degree) [11]. This large difference may be attributed to the fact that our patient collective was treated by regional abdominal hyperthermia versus the whole body hyperthermia applied in the other study.

In most hyperthermia analyses of ovarian cancer patients, chemotherapy-induced myelosuppression was the major toxic effect [8]. Rates of 50% to 65% of haematological toxicity of all grades are described. Our results are clearly more encouraging, with haematological toxicity being less than 40% and the majority of the cases being of mild grade 1 or 2. However, the actual toxicities of combined hyperthermia and chemotherapy, also depending on the dosage of the chemotherapeutic agents, have to be prospectively evaluated in large phase III trials. Also, this difference in toxicity profile may be assigned to the extent of applied hyperthermia (partial abdominal versus whole body). Nevertheless, we cannot report any lower overall response rates, even if the main body of our patient collective was platinum resistant. The overall response rate of most series ranges between 35 and 38%, which is equivalent to our results [8, 11, 20].

Also congruent with previous reports of Franckena et al. [33], we found a significant relationship between the thermal parameter TRISE (Custom made thermal dose parameter based on ALT50 and duration of heating) and the response rate.

In a large observational study from our institution analysing the efficacy of pegylated liposomal doxorubicin without hyperthermia under routine clinical conditions on 183 ovarian cancer patients, rather equivalent survival dates are demonstrated with the ones of the present study: median PFS and OS were 5.8 months (95% CI 5.1–6.6 months) and 16.6 months (95% CI 13.9–22.6 months), respectively [35].

Since the vast majority (47.1% liver and abdominal wall) of the distant metastases reported were located in the abdominal cavity, they were also affected by the regional abdominal hyperthermia. Furthermore, since the chemotherapy was applied systemically and not only intraperitoneally, the cytotoxic effects were also systemic and potentially efficacious also against distant metastatic sites.

Our analysis shows that hyperthermia can safely be combined with platinum and non-platinum agents in heavily pre-treated patients with relapsed ovarian cancer. We could observe individual responses, so further prospective studies are warranted to investigate the efficacy of this combination therapy. Regional abdominal hyperthermia seems to have a relatively equivalent efficacy with whole abdominal hyperthermia by a lower toxicity profile. The statistically similar survival of platinum-resistant and platinum-sensitive patients, is probably attributable to the small number of all patients; especially the platinum-sensitive ones. Keeping in mind that there is currently no evidence that hyperthermia contributes to any clinical improvement beyond chemotherapy alone, we believe that further trials are warranted to prove the efficacy of RHT treatments in an effort to overcome drug resistance and to increase response to palliative salvage chemotherapy. The toxicity profile of combined treatment regimens in this poor prognostic group of immunosuppressed and myelosuppressed patients should always be considered and counterbalanced in respect to their benefits. The parameter ‘quality of life’ should also be purposed as a relevant study objective.

Declaration of interest: No conflict of interest to declare.

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