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# A pilot study of whole body hyperthermia and carboplatin in platinum-resistant ovarian cancer

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**Abstract**

The aim of this study was to determine whether the addition of whole body hyperthermia (WBH) to carboplatin (CBDCA) can induce responses in patients with platinum-resistant ovarian cancer. 16 pretreated patients with platinum-resistant ovarian cancer were entered on a Systemic Hyperthermia Oncological Working Group (SHOWG) study; (14 patients were eligible with 14 evaluable for toxicity and 12 for response). The patients were treated with WBH (Aquatherm®) 41.8°C×60 min in combination with carboplatin (CBDCA) (area under the curve (AUC) of 8) every 4 weeks. Disease status was evaluated every two cycles. Patients were treated for a maximum of six cycles. One patient had a complete response (CR) and 4 had a partial response (PR). 4 patients had stable disease (SD). 3 patients had progressive disease (PD). 2 patients were unevaluable: 1 had a bowel obstruction shortly after her first treatment; the second patient achieved a CR, but only had one treatment secondary to an idiosyncratic reaction to sedative drugs. 2 patients entered on study were ineligible, as they did not meet criteria for platinum resistance; 1 entered a CR and 1 had SD. Dose-limiting toxicity, which required CBDCA dose reductions, was grade 4 thrombocytopenia. Other toxicities included neutropenia (grade 3/4), and nausea and/or vomiting. Consistent with preclinical modelling, these results suggests that 41.8°C WBH can overcome platinum resistance in ovarian cancer. These observations suggest further investigation of the therapeutic potential of WBH in a group of patients who historically fail to respond to salvage therapies is warranted. 

*Keywords:* Ovarian cancer; Whole body hyperthermia; Platinum resistance; Carboplatin

## 1. Introduction

Over 20 000 cases of ovarian cancer are diagnosed each year in the United States. Although the use of chemotherapy has produced response rates of 60–90%, the majority of women with advanced cancer die of progressive disease, thus highlighting the need for improved therapies. In this regard, carboplatin (CBDCA), a key therapeutic drug for ovarian cancer, has been shown to have its cytotoxic effects enhanced preclinically by hyperthermia [1–7]. *In vitro* studies have shown that hyperthermia produces a dose-enhancement effect (i.e. a thermal enhancement ratio of approximately 3 for a 60 min heat exposure) [2,4]. Additionally, assessment of normal tissue toxicity (which for carboplatin is primarily myelosuppression [8]) suggests a significant increase in the therapeutic index, i.e. the ratio of neoplastic to normal tissue cell kill [6,7,9]. Finally, preclinical investigations have shown that hyperthermia can overcome acquired drug resistance [6,10,11].

To explore these laboratory predictions (for the interactions of CBDCA and hyperthermia) a phase I clinical trial was initiated and completed [12]. The study design of this clinical trial allowed a factorial comparison of the biological effects of whole body hyperthermia (WBH) alone, WBH plus CBDCA and

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CBDCA alone. The results of this phase I trial (in heavily pretreated patients) confirmed a myeloprotective effect of WBH with no change in CBDCA pharmacokinetics. Two ovarian cancer patients were entered in this study; these patients had prior platinum therapy and achieved a complete remission with the combination of CBDCA and WBH. Furthermore, a comparison of marker levels in 1 of these patients (i.e. for WBH alone CBDCA alone, and CBDCA/WBH) suggested that WBH enhanced the CBDCA cytotoxicity. It was also demonstrated that WBH increased CBDCA/DNA adduct formation. In the context of the same study, as well as in three later studies [13–15], it was found that WBH induces a series of cytokines, which in part explains the observation that WBH can enhance antineoplastic effects without increasing CBDCA-induced myelosuppression. These cytokines include interleukin (IL)-1β, IL-3, IL-6, IL-8, IL-10, tumour necrosis factor-α, granulocyte colony stimulating factor (G-CSF), and granulocyte macrophage colony stimulating factor (GM-CSF). Another component of this improvement in the therapeutic index is the timing of chemotherapy administration relative to a differential in temperature between the bone marrow and other tissues [16,17], addressed in detail in a series of preclinical [17,18] and clinical investigations [19]. In brief, the concept relates to giving carboplatin at a time (20 min after achieving target temperature) when bone marrow temperature is a few tenths of a degree lower than core temperature. As ovarian cancer rarely affects the bone marrow, this temperature differential effect can be exploited in the clinical setting of CBDCA chemotherapy in combination with radiant-heat WBH.

Because of the encouraging results of these studies, we elected to study CBDCA/WBH in platinum resistant ovarian cancer patients. The study was designed to test the hypothesis that WBH could overcome intrinsic platinum-resistance. A positive result in such a study would justify the inclusion of WBH as an adjunct to chemotherapy in future clinical trials. This report summarises the results of this clinical trial.

## 2. Patients and methods

### 2.1. Patient selection

16 patients with histologically confirmed epithelial ovarian carcinoma were entered on this trial at the Universities of Wisconsin, Amsterdam, and Frankfurt between September 1995 and July 1999. The patients' disease was resistant to cisplatin or carboplatin therapy, or relapsed within 6 months of platinum therapy. Patients were informed of the investigational nature of this study and signed an informed consent form approved by the Human Subjects Committee. This study was approved by institutional review boards at the University of Wisconsin, the University of Amsterdam, the University of Frankfurt, the University of Lübeck, the protocol review committee of the Systemic Hyperthermia Working Oncology Group (SHOWG), and the Food and Drug Administration (USA). Patients were over 18 years of age and had to have a projected life expectancy of at least 12 weeks and an Eastern Cooperative Oncology Group (ECOG) performance status of $\leqslant 2$. Patients were required to have pretherapy baseline physical exams, computed tomography (CT) scans, and CA-125 levels. Patients were not allowed to receive prior chemotherapy within 4 weeks of study enrolment or radiation for 2 weeks prior to study enrolment. No other chemotherapeutic or hormonal agents (with the exception of oestrogen replacement therapy) could be given while the patient was on study.

Patients were required to have adequate bone marrow function (defined as white blood cell $>3\times10$/l, an absolute granulocyte count $\geqslant 1\times10^9$/l cells and a platelet count of $\geqslant 100\times10^9$/l), adequate liver function (total bilirubin $\leqslant 1.5$ mg%, alkaline phosphatase and SGOT (asparate aminotransferase) $3\times$normal; total protein not less than 15% of the lower limit of normal), adequate renal function (creatinine $<1.2$ mg%, and blood urea nitrogen (BUN) $\leqslant 30$ mg%, or creatinine clearance $=60$ ml/min) and normal metabolic parameters (calcium and serum electrolyte values).

Patients with a history of an allergy to lidocaine, malignant hyperthermia associated with general anaesthesia, documented coronary artery disease, angina, congestive heart failure, or serious dysrhythmias were excluded. The protocol excluded patients with severely compromised respiratory status, i.e. any component of full pulmonary function tests being less than 60% of predicted. Neurological bases for exclusion were central nervous system (CNS) involvement by tumour, previous spinal cord or brain irradiation, documented peripheral neuropathy (paraneoplastic or otherwise), or a history of emotional instability.

### 2.2. Treatment plan

All eligible patients were treated in 28-day cycles according to the schema outlined in Fig. 1.

#### 2.2.1. Chemotherapy

The dose of CBDCA was based on renal function using the Calvert formula [20] with an area under the Curve (AUC) of 8; with the dose recalculated prior to each cycle. This represents a dose which has been administered with acceptable toxicity in a prior Phase I WBH + CBDCA trial [12]. Twenty minutes after achieving target temperature, the CBDCA infusion was administered at a constant rate utilising a controlled infusion device over approximately 20 min.

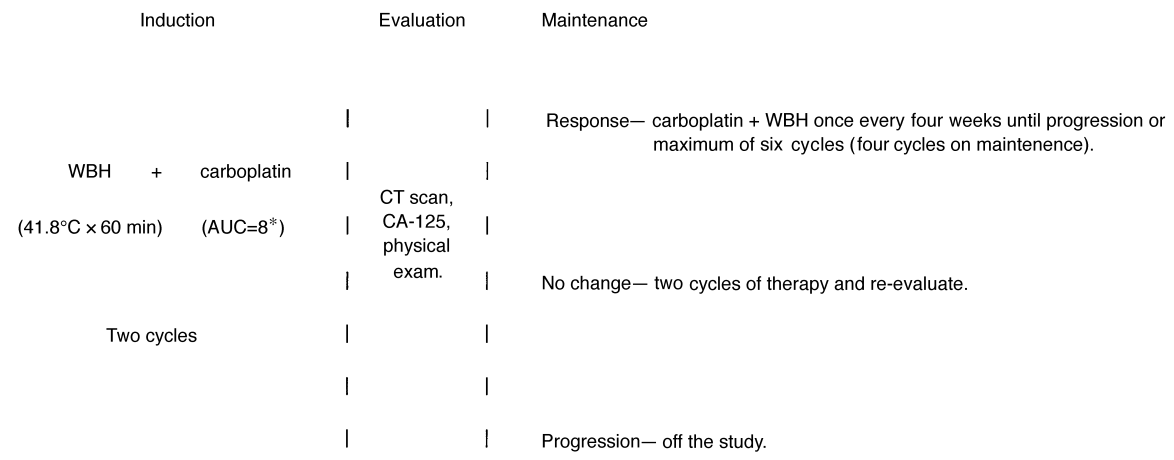


Fig. 1. Schema for the treatment plan. WBH, whole body hypothermia; CT, computed tomography. *Area under the curve (AUC) to be 8 as calculated by the Calvert formula [8].

*2.2.2. WBH treatment procedure and supportive care*

The WBH treatment session procedure is described in detail elsewhere [21]. A hyperthermia treatment session was defined as raising a patient's systemic temperature, (maximum temperature recorded by either rectal or oesophageal/axillary probe) to a designated level, i.e. 41.8°C×60 min. When this temperature was achieved, the patient was removed from the WBH device and systemic temperatures were maintained by keeping a blanket on the patient to minimise evaporative losses. To terminate a hyperthermia treatment, at the end of 60 min, the blanket was removed to allow physiological temperature regulation.

The Aquatherm® system for delivering WBH (patented, Cancer Research Institute, New York) has been previously described [22]. During all hyperthermia treatments, patients received nasal oxygen at 2–6 l/min. Heart rate, respiratory rate, oxygen saturation and cardiac rhythm were continuously monitored. Blood pressure (systolic/diastolic) was monitored at least every 10 min.

Oesophageal, rectal, skin and ambient air temperatures were monitored continuously and recorded at a minimum of 10-min intervals. Temperature probes were calibrated at least monthly against defined external standards (±0.02°C); data were analysed using a linear regression method; corrections were made from 37.0 to 43.0°C. Temperature probes were cleaned using a standard procedure pre- and post-WBH treatment. This consisted of a povidone iodine scrub (United States Pharmacopeia 7.5%), followed by a 20-min soaking in glutaraldehyde, rinsed with tap water and a final rinse with 70% ethanol.

Patients received 0.75 to 1.0 l of intravenous (i.v.) 5% dextrose in 0.25 normal saline per hour alternated with 5% dextrose in 0.5 normal saline plus approximately 7.5 mEq of potassium chloride per litre. Body weight, urinary output (75 ml/h), and electrolytes were monitored to assure fluid and electrolyte homeostasis during and after the procedure. A typical WBH treatment session lasted approximately 4 h, including 1.3 h to reach target temperature, 1 h at 41.8°C, and a 1-h cooling phase. Post-treatment, patients received normal saline 500 to 1000 ml as needed to maintain systolic blood pressures greater than 90 mm Hg. Patients were sedated during WBH with a combination of i.v. thiopental (~4 mg/min) and i.v. lidocaine (~4 mg/min); the details and rationale for this have been previously described [21]. Patients also received incremental boluses of IV midazolam (2–5 mg) and i.v. fentanyl (25–50 μg). Droperidol (1.25–5 mg) was administered during the first 30 min of WBH therapy for both its sedative and antiemetic effects. The aim of sedation was to have a patient who could respond to verbal stimulation and continue spontaneous respirations at a rate greater than 10 breaths/min. Patients were observed after treatment for 20–24 h prior to being discharged. After WBH, some patients received 10–35 mg of metoclopramide i.v. as a prophylaxis against the gastric stasis effect of thiopental. Most patients received ondansetron or granisetron with dexamethazone for emetic prophylaxis.

*2.3. Duration of treatment*

Patients received a second cycle of therapy approximately 28 days after the first cycle if sufficiently recovered from toxicity. Patients were required to have adequate bone marrow function prior to each cycle, and treatment was delayed until bone marrow recovery, defined as WBC $>3\times10^9$/l, an absolute granulocyte count $\geqslant1\times10^9$ and platelet count of $\geqslant100\times10^9$/l. After cycle 2 of therapy, patients were evaluated by CT scan,

CA-125 or physical exam to determine the status of their disease. Responding patients could receive up to four additional cycles of therapy unless there was evidence of progression. Patients with no change received two additional cycles of therapy and then were re-evaluated for further therapy — if there was no change the patient was taken off the study; if there was improvement the patient could receive additional therapy. Patients with progressive disease was removed from study. Other reasons to be removed from the study were the patient's decision to withdraw from study, significant changes in the patient's medical condition which would render the patient unacceptable for treatment in the judgment of the investigator, development of CNS disease while on study, and treatment delay for $\geqslant 4$ weeks.

### 2.4. Evaluation

#### 2.4.1. Toxicity evaluation

Toxicities were assessed using ECOG Common Toxicity Criteria. Dose modifications were applied for haematological toxicity. G-CSF was added to subsequent treatment cycles for patients experiencing febrile neutropenia or WBC counts $<1\times10^9$/l for 7 days in the prior cycle. In cases of febrile neutropenia while on G-CSF, a 25% dose reduction of chemotherapy was initiated on the next cycle of therapy. Patients who had platelet counts $<2\times10^9$/l or a delay in chemotherapy due to thrombocytopenia received a 25% dose reduction in CBDCA. Patients experiencing a delay in the interval of chemotherapy dosing of $>8$ weeks were removed from protocol. Treatment was not given to patients with a creatinine clearance of $<0.83$ ml/s.

#### 2.4.2. Response evaluation

Patients were required to undergo at least two cycles of therapy to be evaluable for response. Patients were monitored with physical exams, standard laboratory evaluation and a CT scan every other cycle. Patients were evaluated for response based on standard criteria for objective regression of measurable lesions. Complete response (CR) required disappearance of all clinically detectable malignant disease without the development of new malignant lesions lasting for at least 4 weeks. Partial response (PR) was defined as a greater than or equal to 50% decrease in tumour size lasting for at least 4 weeks without an increase in the size of any area of known malignant disease or appearance of new areas of malignant disease. This definition must be met in greater than or equal to 50% of the involved organ sites with no organ sites progressing. Stable disease (SD) was defined by no significant change in measurable disease for at least 8 weeks, no increase in the size of any known malignant disease, and no appearance of new areas of malignant disease. Objective progression was defined as a significant increase in the size of lesions present at start of therapy or the appearance of new metastatic lesions.

#### 2.4.3. Statistical considerations

It was postulated that a response rate substantially greater than 10% would be necessary to support our hypothesis. The primary objective of this trial was to provide a preliminary indication that the response rate (complete plus partial) of this regimen in refractory ovarian carcinoma would be substantially greater than 10%. A target of 14 evaluable patients was planned. Confidence intervals for the true response rate for 14 patients were calculated. A minimum of four responses out of 14 would be necessary to demonstrate a response rate significantly greater than 10% at the one-sided 0.05 significance level. There is an 88% chance (power) that at least four responses will occur if the true response rate is 40% or better. An early stopping rule was provided based on the first 8 evaluable patients. If there were no responses in this group, then the regimen would be rejected for lack of efficacy. This screening rule had a sensitivity (probability of continuing) of 94% for a true response rate of 30% and a specificity (probability of stopping) of 66% for a true response rate of 5%. This early stopping rule would have negligible impact on the validity of the confidence intervals above.

## 3. Results

The demographics of the 14 eligible patients entered in the study are listed in Table 1.

### 3.1. Toxicity

There were a total of 44 WBH/CBDCA treatments in the study. The average number of treatment courses per patient was 3.14 (range 1–6); the average number of treatment courses for responding patients was 5.0 (range 4–6). The average AUC for responding (eligible) patients ($n=5$) was 6.72; the average AUC across all treatments ($n=44$) was 6.97. Of the 44 treatments, there were 11 dose reductions based on myelosuppression. Overall, toxicity was not excessive; serial cycles were generally well tolerated. There was no treatment-related mortality. Nausea or vomiting was easily controlled with antiemetics. Myelosuppression was the major toxicity of the trial: there were two episodes of febrile neutropenia. Table 2 summarises the haematological and gastrointestinal toxicities of the trial. One patient (no. 4, see Table 1) with a history of intermittent bowel obstruction developed a complete bowel obstruction (secondary to progressive disease); the patient underwent surgery shortly after her first treatment, and was removed from study.

Table 1
Demographic profile and responses[a]

| Patient no. | Age (years) | PS | Prior therapies (RX) | Number of WBH cycles | TTP (days) | Survival (days) | Response |
|---|---|---|---|---|---|---|---|
| 1 | 60 | 0 | -1-CBDCA/taxol | 6 | 252 | 462 | CR |
| 2 | 66 | 1 | -1-CBDCA/taxol<br>-2-cyclophosphamide/cisplatin | 1 | Placed on new therapy prior to progression | 1056 | Unevaluable[b,c] |
| 3 | 63 | 1 | -1-CBDCA/cyclophosphamide<br>-2-Taxol<br>-3-Taxol/cisplatin<br>-4-Hexamethylmelanin | 2 | 70 | 339 | SD |
| 4 | 45 | 1 | -1-Cisplatin/taxol<br>-2-Cisplatin/cyclophosphamide/doxorubicin | 1 | 30 | 81 | Unevaluable[b] |
| 5 | 60 | 0 | -1-CBDCA/taxol | 2 | 53 | 270 | PD |
| 6 | 48 | 0 | -1-Cisplatin/taxol | 4 | 133 | 448 | SD |
| 7 | 37 | 1 | -1-CBDCA/cyclophosphamide/taxol | 4 | 161 | 283 | PR |
| 8 | 59 | 0 | -1-CBDCA/taxol | 2 | 83 | 252 | SD |
| 9 | 40 | 1 | -1-Cisplatin/taxol<br>-2-CBDCA/endoxan | 5 | 153 | 405 | PR |
| 10 | 65 | 1 | -1-Cisplatin/cyclophosphamide<br>-2-CBDCA/cyclophosphamide<br>-3-Topotecan | 4 | 142 | 331 | SD |
| 11 | 55 | 0 | -1-CBDCA/taxol | 4 | 114 | 153 | PR |
| 12 | 44 | 1 | -1-CBDCA/taxol<br>-2-CBDCA/cyclophosphamide | 2<br>2 | 60<br>60 | 124<br>124 | PD<br>PD |
| 13 | 53 | 2 | -1-CBDCA/cyclophosphamide<br>-2-Cisplatin | 1 | 30 | 134 | PD |
| 14 | 40 | 0 | -1-CBDCA/taxol | 6 | 188+ | 188+ | PR |
| Mean (range) | 53 (37–66) | 0–2 | | Total = 44 | | | 1 CR<br>4 PR<br>4 SD<br>3 PD<br>2 Unevaluable |

CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; TTP, time to progression after WBH treatment (in days); PS performance status; CBDCA, carboplatin; WBH, whole body hyperthermia.

[a] 2 additional patients (age 52 and 48 years) were entered on the study who were ineligible as they did not fulfil criteria for platinum resistance. Both were pretreated (three prior regimens including platinum and taxol): 1 achieved a CR (182 days duration) and the other had stable disease (102 days duration).

[b] Patients received only one treatment therefore they are unevaluable. Patient no. 2 was found to have entered a CR by CT scan and CA-125 criteria. Patient no. 4 had a PD immediately after her first treatment.

[c] Patient was found to have an idiosyncratic reaction to sedative drugs post WBH.

Table 2
Toxicity: haematological and gastrointestinal[a]

| Toxicity | Per cent incidence toxicity | | | |
|---|---|---|---|---|
| | Grade[b] | | | |
| | 1 | 2 | 3 | 4 |
| WBC | 16 | 34 | 18 | 14 |
| Platelet | 7 | 18 | 25 | 25 |
| RBC | 11 | 39 | 14 | 9 |
| Nausea/vomiting | – | – | 2 | 2 |
| Diarrhoea | 2 | 5 | – | – |
| Weight loss | – | 2 | – | – |
| Dehydration | 2 | 2 | – | – |

ECOG, Eastern Co-operative Oncology Group; CBDCA, carboplatin; WBH, whole body hyperthermia; WBC, white blood cell; RBC, red blood cell.

[a] $n = 44$ treatments (CBDCA/WBH).

[b] ECOG Common Toxicity Criteria.

We had no cardiac, pulmonary or thermal (e.g. burns) complications during the course of this study; WBH was generally well tolerated. Toxicity related to WBH included four episodes of mucosal herpes infection, which was readily responsive to valcyclovir (GlaxoWellcome, NC, USA). There were two episodes of post-WBH low grade fevers lasting approximately 24 h. A total of five urinary tract infections were seen in 2 patients, as well as one headache (grade 1) and three episodes of diarrhoea (grade 1 or 2) seen in 2 patients. One patient (no. 2, see Table 1) was not arousable for a period of 6 h post-WBH. All laboratory parameters for this patient were within normal limits. An emergency head CT scan was performed 3 h after WBH and was found to be unremarkable. Six hours after WBH, the patient suddenly became alert and was found to have a normal neurological exam including mental status testing. This

unusual phenomenon had not been previously observed in the 15 year experience with radiant heat WBH (including over 2000 WBH treatments). Subsequent history from the patient's family revealed that a similar idiosyncratic reaction was seen, i.e. a prolonged unarousable state after elective surgeries involving general anaesthesia. It was elected to remove this patient from study after her first treatment. This patient, who by protocol rules was not evaluable for response, was, however, restaged 4 weeks later by CT scan (see responses section below).

#### 3.1.1. Responses

Table 1 summarises the responses seen in the context of this trial. There was one CR, four PR, and four SD. 2 patients described in detail in the toxicity section above were not evaluable because they received only one cycle of therapy. One of these patients (no. 2) was found by CT scan, physical exam, and CA 125 criteria to have entered a CR. The patient embarked on additional therapy prior to the establishment of progressive disease, which made her unevaluable with regard to time to progression (TTP). All CRs and PRs recorded in Table 1 were confirmed both by CT criterion and by physical exam. Patient numbers 1, 3, 9 and 11 had positive CA 125 markers; their prospective marker values were consistent with the responses reported. Patient no. 3 was found to have significant improvement, i.e. minor response, in her hepatic disease (less than a PR), but ultimately progressed by physical exam. Of the responding patients, i.e. numbers 1, 7, 9, 11 and 14 pre-WBH/CBDCA therapy consisted of standard dose platinum agents. (The number of platinum cycles prior to study entry were: six cycles of CBDCA patient no. 1; six cycles CBDCA patient no. 7; one cycle cisplatin and six cycles CBDCA patient no. 9; six cycles CBDCA patient no. 11; and three cycles CBDCA patient no. 14). 2 patients entered in this study were not eligible as they were not platinum resistant by the study criteria; one had a CR and the other SD (see footnote to Table 1). These patients were included in the toxicity evaluation. These data, taken collectively, demonstrate a minimum of five responses in 14 eligible patients, i.e. a response rate of 35.7% with a 90% confidence interval of 15.3–60.9%.

## 4. Discussion

Several preclinical studies have demonstrated the ability of hyperthermia to overcome platinum resistance [6,10,11]. Speculation regarding the molecular basis for this phenomenon includes increased cellular accumulation of drug, increased adduct formation, and inhibition of DNA repair. In this regard, increased CBDCA adduct formation induced by WBH has been previously demonstrated clinically [12]. Relative to DNA repair, detailed studies *in vitro,* as well as in a clinical trial, support the hypothesis that WBH sensitises cells to DNA-damaging agents by blocking the resynthesis of nicotinamide adenine dinucleotide (NAD) consumed for adenosine diphosphate (ADP)-ribose polymer synthesis and thereby limiting polymer synthesis and cellular recovery [23]. It was in this context that this clinical trial was conceived to specifically address the question of platinum resistance by rechallenging platinum-resistant ovarian cancer patients with CBDCA in combination with WBH. At the time of the initiation of this study, it was anticipated that study accrual would be problematic. Clearly, extrapolating from preclinical data (reviewed in the introduction) that suggested that 41.8°C hyperthermia can overcome platinum resistance required a significant leap of faith for both patients and referring physicians. Hence, the study design summarised above, in accordance with the suggestions of institutional review boards, included both an early stopping rule as well as a limited projected patient population (i.e. 14 subjects).

The toxicity encountered in the course of this study was generally related to the extent of prior therapy. In general, the patient population in this study was heavily pretreated. The application of modelling recently developed by Egorin's group (for ovarian cancer patients) [24] predicts ($P=0.05$) at least an 80% incidence of grade 3 or greater myelosuppression for our patient population (based on AUC, starting platelet count and performance status). The haematological toxicity observed, resulting in dose reductions in 25% of treatment courses, was therefore not in excess of that which would be expected. It is of parenthetical interest to note that, in a controlled clinical trial, the addition of WBH to CBDCA was shown to reduce myelosuppression [12]. This was thought to be due to WBH induction of a series of cytokines including IL1-β, IL-6, IL-8, IL-10, and G-CSF peripherally [13,15] and, at the level of the bone marrow, IL-3 and GM-CSF [14].

We observed five responses (1 CR, 4 PR) in 12 evaluable patients (not including one minor response, as well as two CRs, that were either not evaluable or eligible by protocol criteria). 4 patients were observed to have SD. As noted above, the average AUC across treatments for eligible responding patients ($n=5$) was 6.72. Relevant to these results, it is noteworthy that Jodrell and colleagues [25] study of the relationship of AUC to response demonstrates that an AUC above 5 to 7 mg/ml×min does not improve the likelihood of response in ovarian cancer. Thus, these data (with a 90% confidence interval of 15.3–60.9%) provide putative clinical evidence showing that hyperthermia (i.e. WBH) can overcome platinum resistance in ovarian cancer. We believe this trial provides a basis for further clinical exploration of this multimodal approach.

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