Phase II study of carboplatin and whole body hyperthermia (WBH) in recurrent and metastatic cervical cancer

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Received 7 June 2004
Available online 29 September 2004

Abstract

Objective. Hyperthermia enhances carboplatin cytotoxicity preclinically, and clinical studies have shown radiant heat Whole Body Hyperthermia (WBH) to be safe. In this study, the efficacy and toxicity of the combination of 41.8°C WBH and carboplatin in recurrent and/or metastatic cervical cancer were explored.

Methods. Recurrent and/or metastatic cervical cancer patients were treated with 41.8°C WBH and concurrent carboplatin, cycled every 28 days (max. 6 cycles).

Results. Twenty-one of 25 participants were evaluable for response: one complete remission, six partial responses, stable disease in nine patients and progression in five, leading to a response rate of 33%. Three of four evaluable chemotherapy pre-treated patients progressed, while this was seen in only 2 of 17 chemotherapy-naive patients. The median survival is 7.8 months (range 1.3 to 43+) and no patients were lost to follow up. Grades 3/4 toxicities were common: leukopenia in 35%, thrombopenia in 61% and anemia in 22% of all treatments. Excessive, partly reversible renal toxicity was seen in two patients (grades 3 and 4).

Conclusion. The efficacy of WBH and carboplatin in recurrent and/or metastatic cervical cancer seems comparable to that of other palliative chemotherapy regimens in this disease. The considerable toxicity, though largely manageable, includes unexpected and severe unacceptable renal toxicity. This regimen seems less suitable for palliative care.

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Keywords: Carboplatin; Cervical carcinoma; Whole body hyperthermia

Introduction

Cervical cancer represents a substantial health problem in most Western countries, with an incidence of 9 per 100,000 females every year in the US and an overall 5-year survival of 70%. In spite of initial remission, a substantial number of patients develop a recurrence. In this situation, treatment options are often limited to palliative chemotherapy because of irresectability, previous irradiation or metastatic disease.

Cisplatin remains unchallenged as standard chemotherapy for advanced cervical cancer, even though overall response rates are only 18–31% [1,2]. Moreover, these responses tend to be short-lasting (4–6 months), with a median survival of only 6–9 months. In previously irradiated areas, response rates are even lower, with an upper limit of 22%. Metastases outside the previous radiotherapy field are more likely to respond to cisplatin, with response rates between 33% and 73% [3,4]. Although response rates of combination chemotherapy have occasionally been shown to be higher than those of single agent cisplatin, increased toxicity and lack of

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survival have so far not led to combination chemotherapy as standard of care [5,6]. Possibly, publication of the full paper of the encouraging data of the randomized GOG—study of topotecan and cisplatin versus single agent cisplatin—will change that [7].

The adverse effects of cisplatin are considerable, especially in view of the marginal palliative results achieved. Therefore, studies have been performed with carboplatin, which has a better toxicity profile, and response rates that are in the range of those seen with cisplatin [8].

Hyperthermia (HT) is a treatment technique which can be effective in cancer in combination with other treatment modalities. Preclinical studies show that there is clear thermal enhancement of cytotoxicity for platinum derivatives (approximately 3- to 4-fold) and that HT can overcome acquired drug resistance [9,10]. In a phase III clinical trial, Van der Zee et al [11] have shown a survival benefit for HT and radiotherapy (RT) in comparison with RT alone for early cervical carcinoma. Phase II studies of weekly loco-regional HT and cisplatin show encouraging response rates for patients with previously irradiated recurrent cervical carcinoma within the pelvis [12,13]. However, local—regional hyperthermia is limited to patients with local disease only; in disseminated disease, whole body hyperthermia (WBH) may be a treatment strategy. This excludes cisplatin as a drug of choice because of enhanced renal toxicity with WBH [14,15].

Radiant heat WBH has been shown to be safe and feasible in combination with carboplatin [16,17]. The clinical results in these studies are consistent with the preclinical predictions of enhanced cytotoxicity without enhancement of carboplatin myelosuppression or other side effects.

In summary, hyperthermia enhances the cytotoxicity of carboplatin, which is an active drug in cervical cancer, and it is feasible to treat cancer patients with WBH and carboplatin. This provides a strong rationale for further evaluation of this combination. In this prospective phase 2 study, the efficacy and toxicity of the combination of 41.8°C WBH and carboplatin in recurrent and/or metastatic cervical cancer were explored.

**Patients and methods**

**Patient selection**

Eligible patients were required to have histologically or cytologically confirmed cervical cancer. The disease had to be locally advanced or disseminated, not amenable to surgery, radiotherapy, or local hyperthermia with curative intent. Patients were informed of the investigational nature of this study, which was approved by the IRB. All patients gave written informed consent. The ECOG performance status had to be 0, 1, or 2 and the projected life expectancy at least 12 weeks. The age was between 18 and 60 years.

Pre-treatment with chemotherapy for the primary tumor was allowed, but only after chemotherapy became standard first-line treatment in 1999.

Patients required an adequate bone marrow function (defined as WBC $\geq 3 \times 10^9$/l, an absolute granulocyte count $\geq 1.5 \times 10^9$/l cells, a platelet count of $\geq 100 \times 10^9$/l and hematocrit $\geq 32\%$), adequate liver function (total bilirubin $\leq 26 \mu$mol/l, alkaline phosphatase (unless due to bone disease) and SGOT $\leq 3 \times$ upper limit of normal; total protein not less than 15% of lower limit of normal) adequate renal function (creatinine $< 107 \mu$mol/l, and BUN $\leq 11 \mu$mol/l, or creatinine clearance $\geq 60$ ml/min) and normal metabolic values (Ca $\leq 2.75$ mmol/l; Na 130–150 mmol/l; K 3.0–5.0 mmol/l). Heart disease was ruled out by dobutamine-induced stress cardiac ultrasound, and lung function had to be at least 60% of predicted values. The protocol excluded patients with major neoplastic involvement of the liver (more than 33% replacement of liver by tumor), and other major disease that might interfere with treatment protocol.

**Treatment**

The dose of carboplatin, calculated prior to each treatment, was based on renal function using the Calvert formula with an AUC of 6 mg/ml/min. All patients were treated in 28-day cycles with carboplatin and WBH, with a maximum of six courses. Adequate bone marrow function was required prior to each cycle. Treatment was delayed until bone marrow recovery, defined as WBC $\geq 3 \times 10^9$/l, an absolute granulocyte count $\geq 1 \times 10^9$ and platelet count of $\geq 100 \times 10^9$/l. After delay because of insufficient WBC recovery, G-CSF would be added in the next cycle. G-CSF (5 µg/kg) was also initiated if during the previous cycle neutropenic fever occurred or WBC $< 1 \times 10^9$ longer than 7 days. A carboplatin dose reduction of 25% was applied if platelets were $< 20,000$ at any point during the previous cycle, or after treatment delay due to inadequate platelet recovery.

Reasons to be removed from study were the patient’s decision to withdraw, progressive disease, treatment delay $> 4$ weeks, and significant changes in the patient’s medical condition which would render the patient unacceptable for treatment in the judgement of the investigator.

WBH treatment was defined as raising the patient’s temperature to 41.8°C with the Aquatherm© radiant heat device (patented, Cancer Research Institute, New York; Fig. 1). This target temperature was maintained for 1 h. Patients were sedated with a combination of thiopental, midazolam, and fentanyl with lidocaine [18], and all vital signs were continuously monitored by an anesthesiologist. Ten minutes after reaching target temperature, carboplatin was administered over approximately 20 min. A WBH treatment would typically last some 3–4 h, including 80 min to reach target temperature, 1 h at 41.8°C and 30 min

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**References**


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1. WBH treatment device.
cooling phase. Details about the Aquatherm® system and treatment procedure have been published [19].

Evaluation

Toxicity

Patients were assessed weekly for side effects, including hematology and chemistry. Toxicity was graded using NCI Common Toxicity Criteria (http://ctep.info.nih.gov/reporting/ctc.html).

Response

To be evaluable for response, a minimum of two cycles of therapy was required. Patients were evaluated by way of clinical examination and serum tumor markers (if applicable, SCC-Ag for squamous cell cancer and CA-125 for adenocarcinoma) every cycle and CT scan every other cycle. Evaluation for response was based on standard criteria for objective regression of measurable lesions [20]. Progressive patients were withdrawn, responding patients could continue, stable patients were given two more cycles. The maximum number of cycles was six.

Statistical considerations

The clinical level of interest was decided to be a response rate of at least 20%. A target of 14 evaluable patients would be entered in the first stage. If no responses were recorded, the study would be terminated. Under these conditions the rejection error is 5% [21]. If at least one response was observed additional, up to a total number of 25 patients would be treated.

Results

A total of 25 patients was included in this study, with a median age of 45 (range 31–57). Eighteen patients had squamous cell carcinoma, five had adenocarcinoma and two patients had adenocarcinoma in situ.

Fig. 1. Aquatherm® radiant heat device (patented, Cancer Research Institute, New York).

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Note. radioth: radiotherapy; chemoth: chemotherapy; SD: stable disease; PR: partial response; CR: complete response; PD: progressive disease; NE: not evaluable; TTP: time to progression in months counted from study entrance; NA: not available.
carcinoma and two patients were diagnosed with adenosquamous carcinoma. The median number of disease sites was 3 (range 1–5). Six patients had been treated with chemotherapy for their primary tumor and 22 had undergone radiotherapy (Table 1). A total of 82 courses were administered, with a median of 3 per patient (range 1–6).

All patients were evaluable for toxicity and survival, and 21 were evaluable for response. Four patients were not evaluable for response since they had only received one treatment for various reasons: one patient died of early progression, one patient refused further treatment, and two patients experienced severe renal toxicity.

**Efficacy**

Table 1 summarizes the best responses seen in the 21 evaluable patients. One complete remission (CR) and six partial responses (PR) were confirmed by CT scan (Fig. 2), for a response rate (RR) of 33% (95% confidence interval 13–53%). Nine patients were stable during treatment (SD) and five progressed (PD) within 8 weeks after start of treatment.

If these outcomes are arranged by pre-treatment, one out of four evaluable chemotherapy pre-treated patients had a PR, and three a PD. Six of 17 chemotherapy-naive patients had a response, nine were stable, and two showed PD as best response.

Of those patients evaluable for tumor markers (CA125 for adenocarcinoma and SCC-Ag for squamous cell carcinoma), all responding and progressing patients had marker values that were consistent with their clinical response. Of the nine stable patients evaluable for tumor markers, five showed a substantial marker decrease (>50%) and one had an increase (>50%). Three of those five stable patients with a marker remission had a remarkable reduction of their pain complaints.

The seven responding patients were treated with an average of 5.1 cycles, the stable patients 3.6 cycles, and the patients who progressed were treated with 2.0 cycles. With no patients lost to follow up, the median progression-free survival for all 25 participants is 5.3 (range 0.5 to 43+) and the median overall survival is 7.8 months (range 1.3 to 43+) (Fig. 3).

**Toxicity**

The main toxicity was myelosuppression, with grades 3–4 leukopenia in 35% of all cycles, grades 3–4 thrombocytopenia in 61% and grades 3–4 anemia in 22% of all cycles (Table 2). Major bleeding episodes did not occur and neutropenic fever was rare (seven episodes in five patients). Most of the patients received blood transfusions, based on fairly standard criteria, but no record was kept of the number of transfusions per patient. Almost 37% of the treatments was followed by nausea, 34% by vomiting, but these were mostly grade 1 or grade 2.

Besides grades 1 and 2 self-limiting renal toxicity in 20% of all cycles, two patients developed excessive renal toxicity. Both patients suffered rapid deterioration of renal function after their otherwise uncomplicated first course. The first patient had a normal creatinine clearance of 126 ml/min which dropped to 5.7 ml/min 5 days after treatment. Hemodialysis was necessary for 3 weeks, after which renal function partially recovered to a clearance of 30 ml/min. Renal biopsy revealed acute tubular necrosis without specific changes. The creatinine clearance of the second patient dropped from 68 to 13.5 ml/min 5 days after treatment. She recovered to 50 ml/min. No differ-

![Fig. 2](image1.png)  
**Fig. 2.** Computed tomographic studies of liver metastases at baseline (panel A), after two cycles (panel B) and after six cycles (panel C) WBH-carboplatin in the same patient. The number and size of the metastases decrease, while some become necrotic.

![Fig. 3](image2.png)  
**Fig. 3.** Overall survival and progression-free survival from start of study. 4 patients are still alive at 12, 27, 29 and 43 months.
ences which might explain this side effect in these two patients were seen in carboplatin dose, blood pressure, heart rate, urine output or sedative, or analgesics dose during treatment compared to the other patients, nor were there any signs of hydronephrosis.

Painless self-limiting blisters were seen in three patients (Fig. 4), possibly due to pressure on the affected skin during treatment. The protocol was changed after which blisters did not recur. One patient stayed somnolent after her second treatment. A cerebral CT scan did not reveal any lesions and she recovered within 6 h. The next four courses were uncomplicated.

The most debilitating side effect for most patients was fatigue, even though this was rarely grade 3. A total of four urinary tract infections were seen in three patients, three episodes of diarrhea (grade 1) in three patients, seven constipations in three patients and two uncomplicated episodes of dehydration in two patients. One patient developed a previously undiagnosed mood disorder (grade 4) and attempted to commit suicide after her third course. Alopecia was seen in one patient.

A total of 11 courses were administered with a dose reduction (10 patients) and 18 treatment delays were necessary (13 patients), mainly because of myelosuppression (6) and logistical problems (11), for example, unavailability of anesthesiological personnel. Seven evaluable patients did not have any delay or dose reduction.

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Discussion

Several preclinical studies have shown thermal enhancement of carboplatin cytotoxicity [9,10], and a survival benefit was seen for hyperthermia in combination with radiotherapy in cervical cancer [11]. Moreover, loco-regional hyperthermia and cisplatin showed encouraging results in recurrent cervical cancer [12,13]. It was in this context that this clinical trial was initiated, in which the combination of carboplatin and WBH was evaluated in 25 patients with disseminated cervical cancer. Carboplatin was the chemotherapeutic agent of choice because of its previously suggested feasibility in combination with WBH without enhancement of toxicity.

The majority of patients suffered considerable side effects. Even though most toxicity was fairly predictable and clinically manageable, two patients experienced severe renal insufficiency within 5 days after their first course, in one case even necessitating temporary hemodialysis. Even though such serious renal failure has not been described before with carboplatin and WBH [17,22] (and personal communication HI Robins 2002), the temporal relationship between treatment and onset of toxicity suggested a causal relationship, which was supported by the fact that no correlation was found with other parameters. Single agent carboplatin has only very rarely been associated with renal toxicity, mostly in cisplatin pre-treated patients [23]. One of our two patients with renal failure was indeed cisplatin pre-treated. Although it cannot be excluded that the incidence of severe renal toxicity in this patient cohort was purely coincidental, rather than a consequence of WBH, the extreme rarity of such toxicity in carboplatin-only treated patients led us to the conclusion that an as yet unexplained WBH side-effect was most likely responsible.

The response rate of 33% is comparable to that seen in other phase II studies of carboplatin without WBH [8]. Besides this response rate, five stable patients showed a minor response, defined as a tumor marker decrease of at least 50%, and three of those patients had a remarkable pain reduction. Taken together, almost half of all patients seemed to benefit from treatment (the seven responding patients and the five stable patients with ‘marker remission’). The median time to progression, however, was a disappointing 5.3 months, with half of all patients succumbing to disease within 8 months. This is hardly offset by the few patients with a longer lasting response, especially in view of the duration of treatment (almost 1 month per cycle) and associated toxicity in this palliative setting.

During the trial period, standard practice changed to include cisplatin-based chemotherapy in the first line treatment of cervical cancer. Six patients in this study were cisplatin-pre-treated and three of them progressed during the first 8 weeks. It should be noted that two of the other three pre-treated patients were not evaluable for response because they received only one cycle, which may also be associated with tumor non-response. In contrast, early progression was
seen in only two of the 17 chemotherapy-naive patients. It is obviously impossible to draw conclusions with such limited numbers, but there is a definite suggestion of reduced efficacy in cisplatin-pre-treated patients.

In conclusion, although WBH treatment with carboplatin is feasible in the majority of patients with recurrent and metastatic cervical cancer, the unpredictable and very severe renal toxicity that occurred in two patients precludes further development of this treatment-strategy in this group of patients. The short time to progression and the possibly lower response rates in cisplatin-pretreated patients have contributed to this decision, in spite of reasonable response rates and clinical benefit in chemotherapy-naive patients.

Acknowledgments

Partly supported by unrestricted grants of Rhône-Poulenc Rorer (now Aventis Pharma), Bristol-Myers Squibb and Asta Medica.

We thank Dr C.Y. Nio of the Department of Radiology for assistance with the assessment of the CAT scans. The staff of the Department of Anaesthesiology have been crucial in the execution of the WBH treatments, and their contribution is gratefully acknowledged. Prof. HI Robins from the University of Wisconsin is gratefully thanked for his advisory role both in the preparation and in the implementation of the protocol.

References