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Short Communication

Ifosfamide, Carboplatin and Etoposide (ICE) Combined with 41.8°C Whole Body Hyperthermia in Patients with Refractory Sarcoma

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Two earlier studies resulted in the design of a phase II trial of 41.8°C (× 60 min) extracorporeal whole body hyperthermia (WBH) with ICE, i.e. ifosfamide (5 g/m²), carboplatin (300 mg/m²), and etoposide given with WBH, as well as, day 2 and 3 post-WBH (100 mg/m²) for adult patients with refractory sarcoma. 12 patients entered this trial; all were evaluable. 8 patients had a history of prior chemotherapy associated with disease progression. Following WBH/ICE, 7 partial remissions were observed (58%); 3 patients experienced disease stabilisation; the aforementioned 10 patients each received four cycles of therapy. 2 patients exhibited progressive disease. Episodes of WHO graded (grade 3; grade 4) toxicity observed included: anaemia (2;2); leucopenia (5;7); thrombocytopenia (1;6); renal (0;1). Other toxicities (grade 1 and 2) included: anasarca, diarrhoea, ventricular arrhythmias, pressure sores, and perioral herpes simplex. Copyright © 1996 Elsevier Science Ltd

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INTRODUCTION

PRECLINICAL STUDIES in our laboratory have focused on hyperthermic enhancement of various genotoxic chemotherapeutic agents [1–3]. It has also been observed that hyperthermia combined with ifosfamide (IFO) or carboplatin (CBDCA) significantly enhances neoplastic cell kill without a concomitant rise in normal cell toxicity [2, 4, 5]. The basis for the enhancement of neoplastic cell kill, in part, may relate to increased cellular drug penetration as well as overcoming acquired drug resistance [2, 5, 6]. The relative lack of toxicity, i.e. myelosuppression, observed in such studies may reside in the induction of cytokines, as well as the differential heating of the bone marrow during whole body hyperthermia (WBH) [7–10].

Relevant to the previous discussion, clinical 41.8°C WBH has cytoreductive potential, is non-myelosuppressive, and can potentiate the tumoricidal effects of specific cytotoxic agents [11]. Hence, its use as part of a combined modality approach, as suggested by laboratory investigations, is an attractive strategy. Such an approach would require that WBH would not significantly increase chemotherapy-related toxicity. In this regard, Robins and associates in 1993 first provided putative evidence that the aforementioned preclinical predictions for 41.8°C WBH and CBDCA were relevant to clinical practice [8]. These investigators, utilising a radiant-heat technology for WBH, obtained dramatic clinical responses, while demonstrating no increase in chemotherapy related toxicity (with CBDCA doses as high as 575 mg/m²). Corollary studies demonstrated WBH induced increases in CBDCA–DNA adduct formation [8], as well as cytokine induction [7, 12]. There were no WBH induced changes in CBDCA pharmacokinetics. In a subsequent trial, Wiedemann and colleagues [9] extended this approach, using extracorporeal WBH in combination with IFO and CBDCA. As predicted by the earlier clinical experience [8] with single agent chemotherapy (i.e. CBDCA), myelosuppression was unexpectedly low. The dose limiting toxicity was renal. The interpretation of results from this trial was complicated by the use of a haemodialyser, which effectively reduced IFO levels by 30%.

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In order to explicate further the interactions of chemotherapy and WBH, a pilot study in adult patients with sarcoma was designed and initiated. Extracorporeal WBH utilising a heat exchanger (rather than a haemodialyser) was combined with CBDCA, IFO and etoposide (VP-16). The report that follows summarises the toxicity, response data, as well as our assessment of this combined modality approach.

PATIENTS AND METHODS

Patient selection

Patients were required to have histologically confirmed advanced and/or metastatic sarcoma with at least one measurable lesion progressing under conventional therapy. Only patients with a World Health Organisation (WHO) performance status of 2 or better, and a life expectancy of at least 3 months, were included in the study. Patients older than 65 years and/or with evidence of central nervous system metastasis were excluded. Laboratory prerequisites and pretreatment evaluation have been previously described [8, 9]. The demographic profiles of the 12 patients studied are listed in Table 1. The patients were treated between April and September 1994. The mean age was 38 years (range 17–57). Written informed consent was obtained from all patients. The study was approved by the Ethics Commission of the Medical University of Lübeck.

WBH treatment procedure

WBH (41.8°C for 60 min) was achieved by reinfusion of extracorporeally heated blood, a method modified after Parks and Smith [13]. The blood was warmed up in a heat exchanger (Level One, Rockland, Massachusetts, U.S.A.). The roller pump driven volume flow of the warmed (up to 45.5°C) reinfused blood was adjusted to 700 ml/min. During all hyperthermia treatments, the patients were under general anaethesia (~4 h). Heart rate, stroke volume, respiratory rate and cardiac rhythm were continuously monitored. Cardiac output was calculated every 10 min via Swan Ganz catheterisation. Arterial blood pressure was monitored in the radial artery. Rectal temperature and pulmonary artery temperature were continuously recorded. Temperature probes were calibrated against a mercury thermometer standard (sensitivity ± 0.05°C). Patients received high dose heparin during the WBH treatment. They received i.v. 5% glucose in 0.45% normal saline with 10 mEq potassium chloride per litre. The initial fluid rate was 1000 ml/h at the onset of heating; this rate was subsequently adjusted to maintain a urine flow greater than 40 ml/h. All patients needed catecholamines to keep their blood pressure within an acceptable range. Dopamine (i.v.) was begun at 10 mg/h at the start of WBH; 30–50 mg/h was required during the plateau phase (41.8°C). Additionally, noradrenaline (i.v.) 0.1–0.8 mg/h was given during the plateau phase. Electrolyte and Mg^{2+} replacement was adjusted according to the results of serial determinations of blood levels. Forty milligrammes of dexamethasone was administered at the beginning of WBH treatment and again 8 h later. A typical WBH treatment session lasted 4 h, which consisted of 2 h to reach target temperature, 60 min at 41.8°C, i.e. the specified period of hyperthermia, and a 1 h cooling period. Immediately after WBH, patients were returned to an intensive care unit and discharged after at least 24 h observation.

Timing of chemotherapy (Figure 1)

IFO (ASTA Medica, Frankfurt, Germany) was infused (i.v.) over 120 min after 37°C rectal temperature was attained by heating the patient. (The rectal temperature of the patients before onset of heating was between 35 and 36°C.) CBDCA (Bristol-Myers Squibb, New Jersey, U.S.A.) was infused (i.v.) over 90 min after 40°C was attained. Etoposide (Bristol-Myers Squibb) was given (i.v.) over 60 min at target temperature, as well as day 2 and 3 post-WBH. Mesna (Uromitexan, ASTA Medica) was administered i.v. before the start of IFO infusion and every 4 h thereafter (up to 8 h). Each Mesna dose was 20% of the amount of IFO given per day. Granulocyte colony stimulating factor (G-CSF) (Amgen, Inc., California, U.S.A.) was administered s.c. beginning 24 h after the last day of chemotherapy for 5 days. Patients with platelet counts less than 20×10^9/l received platelet transfusions.

Treatment and evaluation protocol

The patients were retreated when they had recovered from all toxicity (i.e. 4 weeks after the last therapy). Three weeks after day 1 of the second treatment, the patients were evaluated by CT scan and physical examination to determine the status of their disease. The treatments were discontinued when disease progression was documented, or after a total of four courses were given. Patients were monitored weekly for toxicity. The WHO common toxicity criteria were used to grade toxicities. Response to the treatment, i.e. complete response, partial response (PR) and stable disease, were evaluated using standard WHO criteria.

RESULTS

Toxicity

Haematological. Myelosuppression was significant, but tolerated. (In retrospect, G-CSF might have been given for more than 5 days to prevent the subsequent neutropenia.) 3 patients had episodes of bleeding related to the extracorporeal WBH treatment procedure. The only infectious complications related to herpes simplex (see *Skin* below). Grade 3 or 4 toxicity included: thrombocytopenia, 7 patients; leucopenia, 12 patients; anaemia, 4 patients. Grade 1 or 2 toxicity included: thrombocytopenia, 4 patients; anaemia, 8 patients.

Renal. Generally, patients had elevated creatinines requiring aggressive hydration for 5 days following WBH. 5 patients demonstrated signs of nephrotoxicity. One patient suffered from severe renal toxicity. The patient developed acute renal failure 5 days after the first cycle of the combined treatment and required haemodialysis. The patient recovered after 11 weeks of dialysis.

Cardiotoxicity. 3 patients were observed to have ventricular arrhythmias. Heart rate and cardiac output of the patients treated with ICE combined with WBH increased with rising core temperature, whereby the heart rate rose considerably more than the stroke volume. In order to maintain stable mean blood pressure, mean pulmonary artery pressure and pulmonary artery wedge pressure fluid substitution and the administration of catecholamines was required. For 34 treatments, the mean systolic pressure was 116.4 ± 10.7 mm Hg pre-WBH and 82.4 ± 8.6 mm Hg at 41.8°C.

Neurotoxicity. 2 patients developed reversible (grade 2) parasthesias of hands and feet.

Gastrointestinal. All patients experienced grade 1 or 2 nausea and vomiting. Diarrhoea was observed up to several days post-WBH. Grade 1 hepatitis was observed in 3 patients.

Table 1. *WBH profile of patients receiving IFO, CBCDA and ETO (ICE) with* 41.8°C

Patient no.	Age/sex	Diagnosis	Tumour site	Prior treatment*	Response to ICE and WBH†	Time to relapse	Survival from start of therapy (as of April 1995)
1	21/m	Synovialsarcoma	Skin met., lung met.	Sur.; RT; IFO, ETO, DOX, AMD, VCR	PR	114 days	217 days
2	32/m	Liposarcoma	Soft tissue met., lung met. bony	Sur.; CYC; DOX, VCR, DTIC	NC	No relapse after 291 days	Alive
3	25/m	Neurofibrosarcoma	Lung met., bony met.	Sur.; RT; IFO, DOX	PR	Relapse after 156 days	206 days
4	52/f	Rhabdomyosarcoma	Right thigh, lung met., LN met.	Sur.; RT; IFO, DOX	PR	Relapse after 246 days	Alive since 299 days
5	33/m	Synovialsarcoma	Soft tissue met., lung met., bony	Sur.; RT; IFO, DOX	PR	Relapse after 117 days	156 days
6	57/f	Rhabdomyosarcoma	Lung met.		NC	No relapse after 223 days	Alive
7	40/f	Sarcoma	Lung	Sur.; RT, CBDCA, ETO, ELD, 5FU	PD	Relapse after 53 days	185 days
8	48/m	Liposarcoma	Left thigh, lung met.	Sur.; RT	PR	No relapse after 201 days	Alive
9	43/m	Leimyosarcoma	Abdominal met., liver met.	Sur.	PD	Relapse after 55 days	Alive since 83 days
10	46/f	Liposarcoma	Abdominal met.	Sur.; RT	NC	No relapse after 112 days	Alive
11	39/m	Leiomyosarcoma	Right thigh, lung met.	Sur.; IFO, ETO, EPI, VIN, CYC, DOX, DTIC	PR	No relapse after 119 days	Alive
12	17/m	Sarcoma	Lung met.	CYC, DOX, VCR, DTIC	PR	No relapse after 120 days	Alive

Sur., surgery; RT, radiation therapy; IFO, ifosfamide; ETO, etoposide; AMD, actinomycin-D; VCR, vincristine; CYC, cyclophosphamide; CBDCA, carboplatin; 5-FU, 5-fluorouracil; ELD, eldsin; VIN, vindesin; DTIC, dacarbazine; EPI, epirubicin; DOX, doxorubicin; met., metastasis.

*All patients receiving chemotherapy had a history of progression while on chemotherapy, i.e. there were no relapses post chemotherapy. †PR, partial remission, NC, no change, PD, progressive disease.

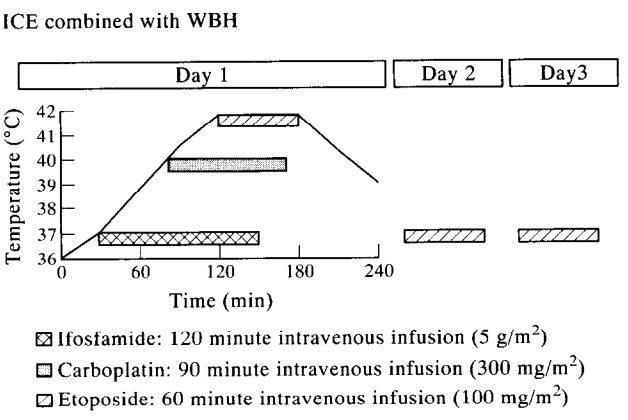

Figure 1. ICE (ifosfamide, carboplatin and etoposide) with whole body hyperthermia (WBH).

Skin. All patients experienced mild anasarca after every WBH treatment (up to 3 days). Perioral herpes simplex occurred in 3 patients. Pressure sores (grade 3) were observed in 3 patients.

Response to therapy.

7 out of 12 evaluable patients receiving ICE plus WBH demonstrated PR, 3 experienced disease stabilisation and 2 exhibited progressive disease after two courses of therapy (Table 1).

DISCUSSION

It is clear that the limited number of patients in this pilot phase II study compromises the validity of the reported response rate of 58%. Indeed, a 95% confidence interval would encompass a response rate of 28–85%. A previous small series of sarcoma patients treated with ICE alone resulted in two PRs in 10 patients (95% confidence 0–50%) [14]. The prior therapy of this group of patients was not specified. The fact that 7 of the 8 patients experiencing PRs in our study had a prior history of progressive disease while receiving chemotherapy (Table 1), is consistent with the supposition that WBH may both enhance cytotoxicity and overcome drug resistance [5, 8, 9].

It was elected not to expand the current series of patients, as the toxicity data accrued was sufficient to convince our group to adopt an alternate technology for delivering 41.8°C WBH. This interpretation of the toxicity data was influenced by a series of 8 patients (mean age 40) with comparable prior therapy treated with ICE chemotherapy at exactly the same doses and schedule (including G-CSF) during the same year this study was conducted. Myelosuppression observed for this non-WBH group was not statistically different from the WBH/ICE patients. This lack of increased myelosuppression in the WBH group in part relates to the induction of cytokines by WBH, which protect against thrombocytopenia and neutropenia. These cytokines include G-CSF, interleukin (IL)-1β, as well as IL-6, IL-8, IL-10 and TNF-α [7, 12].

However, there was no evidence of renal toxicity with non-WBH/ICE treated patients. Indeed, a 95% confidence interval for severe renal toxicity for our current study could extrapolate as high as 39%. Significant renal toxicity complicated our prior study [9], and is traditionally associated with extracorporeal systemic hyperthermia [11]. An explanation for this morbidity undoubtedly relates to a pre-renal state (precipitated by relative hypotension during treatment in spite of cardiotropic support) coupled to the administration of renal toxic chemotherapy, i.e. ifosfamide and carboplatin. It is notable that radiant-heat hyperthermia is not associated with such cardiac compromise of systolic function in the absence of cardiotropic support or diuretics [11], and electrolyte shifts and Mg^{2+} losses associated with extracorporeal WBH do not occur in radiant-heat WBH [11]. In this regard, Robins and associates [8] reported the treatment of 3 patients with a previous history of severe renal failure treated with radiant-heat WBH and high dose carboplatin (575 mg/m²). Two of these patients had a prior history of grade 4 renal toxicity associated with cisplatin. During the reported courses of thermochemotherapy, there was no change in baseline creatinines or creatinine clearances of these patients (unlike our extracorporeal WBH experience). Additionally, other toxicities encountered in our study, which were clearly related to extracorporeal WBH, i.e. diarrhoea, parasthesias, arrhythmias and pressure sores, are not associated with radiant-heat WBH.

In view of the above considerations, the financial costs associated with extracorporeal WBH, and the ultimate need for multi-institutional trials, the University of Lübeck joined the Systemic Hyperthermia Oncology Working Group (SHOWG) [15]. As a group member, we instituted (May 1995) the use of the *Aquatherm* (patent pending) radiant heat WBH device [13] with ICE chemotherapy, as part of pilot-toxicity study (which primarily addresses nephrotoxicity). As of August 1995, 50 ICE/WBH treatments involving 16 patients (with mixed histologies) were completed. There has been no evidence of renal toxicity in any of these treatments. 6 of the subjects were sarcoma patients; a PR has been achieved in 4 of these to date. In view of this positive experience, it is anticipated that, after completion of this pilot study, a randomised group (SHOWG) trial in sarcoma patients will be initiated in the winter of 1996.

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