Ifosfamide, carboplatin and etoposide combined with 41.8 °C whole body hyperthermia for malignant pleural mesothelioma

A. Bakhshandeh a,*, I. Bruns a, A. Traynor b, H.I. Robins b, K. Eberhardt c, A. Demedts c, E. Kaukel d, G. Koschel d, U. Gatzemeier e, Th. Kohlmann a, K. Dalhoff a, E.M. Ehlers a, Y. Gruber a, R. Zumschlinge f, S. Hegewisch-Becker g, S.O. Peters a, G.J. Wiedemann h

a Medical University of Lübeck, Ratzeburger Allee 160, 23538 Luebeck, Germany
b University of Wisconsin, Madison, WI, USA
c Zentralkrankenhaus Bremen-Ost, Bremen, Germany
d AKH Harburg, Hamburg, Germany
e Krankenhaus Großhadern, Großhadern, Germany
f Krankenhaus Trostberg, Trostberg, Germany
g Universitätsklinik Eppendorf Hamburg, Hamburg, Germany
h Oberschwaben Klinik Ravensburg, Ravensburg, Germany

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Abstract

We performed a phase II study combining 41.8 °C whole body hyperthermia with ICE chemotherapy, i.e. ifosfamide (5 g/m²), carboplatin (300 mg/m²) and etoposide (150 mg/m² on days 2 and 3), administered every 4 weeks, for patients with malignant pleural mesothelioma. Of 27 chemonaive, non-metastatic patients enrolled, 25 patients were evaluable for response. Overall response rate was 20% (five partial remissions; 95% CI 8.9–39.1%). Median survival time from the start of treatment for all patients was 76.6 weeks (95% CI 65.4–87.8 weeks). Progression free survival for all patients measured 29.6 weeks (95% CI 24.4–34.7 weeks). One year overall survival was 68% and 2 year overall survival was 20%. Major treatment toxicities included grade 3/4 neutropenia and thrombocytopenia in 74 and 33% of treatment cycles, respectively. One patient died due to sepsis. These promising results are consistent with continued clinical investigation; a phase III clinical trial with whole body hyperthermia as the independent variable has been initiated.

Keywords: Whole body hyperthermia; Chemotherapy; Malignant pleural mesothelioma

1. Introduction

Malignant mesothelioma is the most common tumor of the pleura. Although rare, its incidence is increasing due to prior occupational exposure to asbestos, and this trend is expected to continue until at least 2020 [1]. The incidence of malignant pleural mesothelioma in Europe is 1.6 cases per 100 000. Treatment remains unsatisfactory, with overall survival measuring 12 months or less [2]. Single or combined modality treatments using curative or debunking resection, adjuvant radiotherapy, and adjuvant or palliative chemotherapy have yet to consistently impact on survival [3,4]. A meta-analysis examining 55 phase II trials determined that cisplatin was the most active single chemotherapeutic agent, with a response rate of 18.8%, while cisplatin and doxorubicin was the most active combination, with a response rate of 29.7% [5]. Clearly, improved treatment strategies are needed for this patient population.

Hyperthermia has exerted antitumor effects preclinically and in patients with various malignancies, such as gastrointestinal tumors, lung cancer, and sarcoma [6,7].
Neoplastic cells appear more sensitive to the effects of hyperthermia greater than 41 °C, compared to normal cells [6,8,9]. Mechanisms of the antitumor actions of hyperthermia include inhibition of the DNA repair enzyme poly (ADP/ribose) polymerase, via reduced levels of NAD+, induction of apoptosis and inhibition of neoangiogenesis [6,10,11].

The combination of hyperthermia and carboplatin has demonstrated the ability to overcome platinum resistance in patients with ovarian cancer, while not worsening toxicity [12]. Synergistic growth inhibitory effects have been seen in a pleural mesothelioma cell line when hyperthermia was combined with ifosfamide [13]. Lastly, preclinical data have demonstrated that the sequential use of VP-16 after WBH (in combination with ifosfamide and carboplatin) down regulates glucose related stress protein 78 (GRP-78), which confers resistance to VP-16 [14]. Together, these data provide the rationale for combining radiant heat hyperthermia using the Aquatherm device with ICE chemotherapy in patients with malignant pleural mesothelioma.

2. Materials and methods

2.1. Patient selection

Patients with histologically confirmed advanced malignant pleural mesothelioma enrolled in this trial between April 1999 and February 2001. Patients were informed about the investigational nature of this study and signed an informed consent form previously approved by the Human Subjects Committee. Patients had to be over 18 and below 65 years of age and had to have a projected life expectancy of at least 12 weeks and an ECOG performance status of ≤2. Patients were required to have pre-therapy baseline physical exams and CT scans. No other chemotherapeutic agents could be given on study. Patients were staged using Classification of International Mesothelioma Interest Group [15]. Patients were required to have adequate bone marrow function (defined as WBC > 3000 cells/µl and an absolute granulocyte count ≥1000 cells/µl and a platelet count of ≥100 000 cells/µl), adequate liver function (total bilirubin ≤1.5 mg%, alkaline phosphatase and AST ≤3 x normal; total protein not less than 15% of lower limit of normal), adequate renal function (creatinine < 1.2 mg%, and BUN ≤ 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 anesthesia, 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. Neurologic bases for exclusion were 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.

2.3. Chemotherapy

2.3.1. ICE treatment procedure

Ifosfamide (IFO; ASTA Medica Oncology, Frankfurt, Germany) at 5 g/m² was infused (i.v.) over 60 min after 37 °C rectal temperature was attained by heating the patient. Carboplatin (CBDCA; Bristol-Meyers Squibb, NJ, USA) at 300 mg/m² was infused (i.v.) over 20 min; 10 min after achieving 41.8 °C by esophageal temperature. Etoposide (VP-16; Bristol-Meyers Squibb) at 150 mg/m² was given (i.v.) over 60 min on days 2 and 3 post-WBH. Mesna (Uromitexan, ASTA Medica) was administered intravenously before the start of IFO infusion and every 4 h thereafter for a total of three administrations. Each Mesna dose was 20% (1 g/m²) of the amount of IFO given per day.

The actual body surface area was used to calculate chemotherapy doses; both actual and ideal surface areas were calculated. If actual was < 12.5% above ideal, the actual surface area was utilized. If actual was ≥12.5% above the ideal, the maximum surface area to be used was 2.0.

Granulocyte colony stimulating factor at 5 µg/kg BW per day (Filgrastim; Amgen, Inc., CA, USA) was administered subcutaneously beginning 24 h after the last day of chemotherapy for 5 days. Patients with platelet counts less than 20 x 10⁹/l received platelet transfusions.

2.4. WBH treatment procedure and supportive care

The WBH treatment procedure was defined as raising a patient’s systemic temperature, (maximum temperature recorded by either rectal or esophageal/axillary probe) to 41.8 ± 0.2 °C x 60 min [16,17]. When this temperature was achieved, the patient was removed from the WBH device and systemic temperatures were maintained by keeping a vapor barrier on the patient to minimize evaporative losses. To terminate a hyperthermia treatment, at the end of 60 min, the vapor barrier was removed to allow physiological temperature regulation.

The Aquatherm system for delivering WBH (patented, Cancer Research Institute, NY, NY) has been previously described [18]. During all hyperthermia treat-
ments, 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.

Esophageal, 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 analyzed 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.

Patients received 0.75–1.0 l of intravenous 5% dextrose in 0.25 normal saline per hour alternating with 5% dextrose in 0.5 normal saline plus approximately 7.5 mEq of potassium chloride per liter. 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 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 500–1000 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 [16]. Patients also received incremental boluses of i.v. 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 discharged. All patients received ondansetron or granisetron with dexamethasone for emetic prophylaxis.

2.5. Duration of treatment

Patients received a second cycle of therapy 4 weeks 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 >3000 cells/μl, an absolute granulocyte count ≥1000 cells/μl and platelet count of ≥100 000 cells/μl. Responding patients or those with stable disease (SD) could receive up to 2 additional cycles of therapy, unless there was evidence of progression. Patients with progressive disease (PD) were removed from the study after 2 cycles. Other reasons to be removed from the study were the patient’s decision to withdraw, significant changes in the patient’s medical condition that would render the patient unacceptable for treatment in the judgment of the investigator (e.g., significant progression), development of central nervous system disease while on study, and treatment delay for ≥4 weeks.

2.6. Evaluation

2.6.1. Toxicity evaluation

Toxicities were assessed using the Common Toxicity Criteria (NCI CTC) (National Institute of Health-version 2.0: available from http://ctep.info.nih.gov). All patients were considered evaluable for toxicity.
2.6.2. Response evaluation

Patients were required to undergo at least two cycles of therapy to be evaluable for response. Patients were followed with physical exams and standard laboratory evaluation. Thoracic CT scans were used in all cases to evaluate treatment response and were performed after the second and fourth treatment cycles. All CT scans were reevaluated by an independent radiologist and our centrally radiologist upon completion of the study. The depth of the tumor was measured on contiguous slices obtained at the level of the thickest lesions. The three thickest lesions were chosen as the parameter for response. The determination of the levels of the control scans was adjusted with regard to different landmarks within the mediastinum, depending on the location of the tumor. Complete response (CR) required disappearance of all clinically detectable malignant disease without development of new malignant lesions lasting for at least 4 weeks. Partial response (PR) was defined as \( \geq 50\% \) decrease in tumor size or thickness lasting for at least 4 weeks without increase in size of any area or thickness of known malignant disease or appearance of new areas of malignant disease. Minor response (MR) was defined as a decrease in tumor size or thickness of less than 50\% but greater than 25\% for at least 4 weeks without signs of progression. SD was defined by no significant change in measurable disease for at least 8 weeks, no increase in size of any known malignant disease, and no appearance of new areas of malignant disease. PD was defined as a \( \geq 25\% \) increase in the size or thickness of lesions present at the start of therapy or appearance of new metastatic lesions.

2.7. Statistical planning and analysis

Sample size considerations were based on the overall response rate. We computed 95 percent confidence intervals for response rates of 20, 30 and 40\% assuming sample sizes between 25 and 40 patients. With an overall response rate of 20\% the length of the confidence interval in a sample of 25 patients is approximately 30\% points. Increasing sample size would result in a reduction of the confidence interval to 29, 27 and 25\% points in samples of 30, 35, and 40 patients, respectively. Similar results were obtained with response rates of 30\% and 40\%. Given these results it was decided that the minor reduction of confidence interval width would not justify to increase the sample size beyond 25 patients.

3. Results

3.1. Response to therapy

Twenty-seven patients enrolled into this study from April 1999 through February 2001. A demographic profile of patients is presented in Table 1. The majority of patients enrolled in this study had epithelial histology. Also, most patients had stage III disease. Twenty-five patients were evaluable for response. All patients were evaluable for toxicity.

Table 2 presents response results for the overall patient population. The overall response rate was 20\% (five partial remissions; 95\% CI 8.9–39.1\%), with MRs seen in 12\% of patients and SD occurring in 44\% of patients.

Fig. 2 displays the Kaplan–Meier estimate for overall survival for the study participants. Median overall survival time from the start of treatment for all patients was 76.6 weeks (95\% CI 65–87.8 weeks). Median survival time from initial diagnosis was 83.8 weeks (95\% CI 73.9–93.8 weeks) for all patients. Fig. 3 displays the Kaplan–Meier estimate for progression free survival for the patients evaluable for response in this study. Progression free survival for all patients from the start of treatment measured 29.6 weeks (95\% CI 24.4–34.7 weeks). The 1 and 2 year overall survival rates were 68 and 20\%, respectively, with 5 patients still alive as of October 2002.

3.2. Toxicity

Toxicity data according to the NCI CTC are summarized in Table 3. Myelosuppression was significant but manageable. There was 1 death associated with PD and sepsis. Patients became neutropenic and/or thrombocytopenic between days 7 and 10 after WBH treatment. Two cardiac complications (cardiac arrhythmia
during hyperthermia at 41.3 °C) were observed despite the use of prophylactic lidocaine during WBH. No episodes of heart failure or myocardial infarction occurred.

The data from this ICE/WBH study demonstrated no differences in blood count nadirs for WBH/ICE as compared to reports of patients treated with ICE alone [7,19].

4. Discussion

Treatment for malignant pleural mesothelioma has failed to date to consistently prolong survival, likely due to poor patient selection, pathologic misdiagnoses, and ineffective therapies [3,4]. Surgical resection with pleure-opneumonectomy requires patients with excellent pre-morbid exercise tolerance without dyspnea [3]. Favorable prognostic factors identified in surgical and medical series include pure epithelial histology, good performance status, female gender, absence of lymph node involvement, and absence of leucocytosis [20,21].

Preliminary results from a 1999 meta-analysis that reviewed 55 phase II studies of chemotherapy in malignant pleural mesothelioma identified cisplatin as the most active single agent, with a response rate of 18.8%, and the combination of cisplatin and doxorubicin as the most active regimen, with a response rate of 29.7% [5]. A phase II study of 21 patients treated with the combination of cisplatin and gemcitabine yielded a response rate of 47% and overall survival of 10 months [22]. Follow-up studies of this combination have detected lower response rates of 26 and 16% [23]. Antifolates have also demonstrated activity in phase II trials, with response rates of 25% for edatrexate and 37% for methotrexate [4]. Four patients achieved partial remission in a phase I study of the multitargeted antifolate pemetrexed in combination with cisplatin [24]. As such, a large, international phase III trial, comparing cisplatin alone with cisplatin plus pemetrexed was conducted [25]. In that study of 456 chemonaive patients, antitumor response, time to progression, and median survival were all statistically significantly improved in patients receiving the combination therapy (41% versus 17%, 5.7 months versus 3.9 months, and 12.1 months versus 9.3 months, respectively). Toxicity with this regimen was ameliorated with the use of folate and vitamin B12

<p>| Table 2 | Percent (%) responses in different patient cohorts |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Patient population</th>
<th>RR (%)</th>
<th>RR (%) 95% CI</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>MR (%)</th>
<th>SD (%)</th>
<th>PD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n = 25)</td>
<td>20</td>
<td>8.9–39.1</td>
<td>0</td>
<td>20</td>
<td>12</td>
<td>44</td>
<td>24</td>
</tr>
</tbody>
</table>

n, number of patients; RR, overall response rate; CI, confidence interval; CR, complete response; PR, partial response; MR, minor response; SD, stable disease; PD, progressive disease

| Table 3 | Percent incidencea, toxicityb |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Toxicity grade | 1 | 2 | 3 | 4 |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| WBC | 8.0 | 4.0 | 24.0 | 50.0 |
| Infection | 10.0 | 6.0 | 5.0 | 0.0 |
| Platelet | 18.0 | 22.0 | 15.0 | 18.0 |
| Hgb | 22.0 | 35.0 | 9.0 | 1.0 |
| GI | 13.0 | 8.0 | 1.0 | 0.0 |
| Nausea | 51.0 | 8.0 | 9.0 | 0.0 |
| Vomiting | 41.0 | 4.0 | 4.0 | 0.0 |
| Hepatic | 14.0 | 3.0 | 0.0 | 0.0 |
| Fatigue | 4.0 | 0.0 | 0.0 | 0.0 |
| Skin | 3.0 | 0.0 | 3.0 | 0.0 |
| Renal | 8.0 | 3.0 | 0.0 | 0.0 |

WBC, neutropenia; Hgb, hemoglobin; GI, gastrointestinal

a 47 courses of treatment in 27 patients

b Common toxicity criteria (National Institute of Health) — version 2.0: http://ctep.info.nih.gov

Fig. 2. Overall survival for all patients from start of treatment.

Fig. 3. Progression-free time for all patients from start of treatment.
supplementation [25]. Another novel compound under investigation for its use in mesothelioma is ranpirnase, an antineoplastic ribonuclease derived from frog eggs. In a recent phase II trial of this compound, a median survival of 8.3 months resulted in good prognosis patients [26]. The combination of doxorubicin and ranpirnase is to be tested against doxorubicin alone in an upcoming phase III trial. Lastly, recent studies of immunotherapy using intrapleural interleukin-2 or systemic interferon α-2b have revealed encouraging results that require confirmation [27].

Hyperthermia has enhanced the cytotoxicity of radiotherapy or chemotherapy when used in combination in preclinical models [6,7]. An improvement in the therapeutic index of carboplatin was seen when administered with WBH, with increased adduct formation and simultaneous mitigation of myelosuppression, secondary to the WBH-induced expression of myeloprotective cytokines, such as II-6, II-3, II-8, GCSF, GMCSF, and TNF-α [28]. The ability of hyperthermia to enhance the cytotoxicity of carboplatin was felt related in part to inhibition of DNA NAD+ synthesis, which is the rate limiting substrate of the DNA repair enzyme poly (ADP/ribose) polymerase [10,29]. The preclinical and clinical activity of carboplatin and ifosfamide in the treatment of malignant mesothelioma has been established [13,30,31].

These findings prompted further research into methods of incorporating chemotherapeutic agents with WBH in patients with refractory malignancies. Laboratory investigations detected that the sequential use of VP-16 after Aquatherm WBH (in combination with ifosfamide and carboplatin) produced superadditive cytotoxicity on the basis of down regulating GRP-78, which confers resistance to VP-16 [14]. Clinical evaluation of the Aquatherm radiant heat system and ICE chemotherapy in patients with refractory sarcoma resulted in no significant cardiopulmonary or renal toxicity, and a response rate of 29% and a median survival estimate of 393 days [32]. This is in contrast to the use of cisplatin with hyperthermia, which results in prohibitive nephrotoxicity [33,34]. As such, with clinical benefit demonstrated in patients with refractory soft tissue sarcoma and due to the traditional classification of soft tissue sarcoma with malignant mesothelioma, this investigation using ICE chemotherapy was undertaken in patients with malignant pleural mesothelioma.

Results from our multicenter phase II trial of ICE chemotherapy combined with Aquatherm WBH compare satisfactorily in terms of both overall and progression free survival with recent trials in this setting [22,25,26]. The ICE chemotherapy and WBH treatment was generally well tolerated and its use in this phase II study was associated with a significant 2 year overall survival rate of 20%.

This clinical trial demonstrates the feasibility of performing a large multicenter cooperative group study involving WBH. These findings, taken together with the preclinical studies and earlier clinical studies, support the continued investigation of this multimodality approach in this poor prognosis patient population. We propose the outcome of this study provides a strong foundation for a phase III randomized clinical trial of chemotherapy with and without WBH.

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References