A Systemic Hyperthermia Oncologic Working Group Trial
Ifosfamide, Carboplatin, and Etoposide Combined with 41.8°C Whole-Body Hyperthermia for Metastatic Soft Tissue Sarcoma

A.M. Westermann a G.J. Wiedemann b E. Jager c D. Jager c
D.M. Katschinski b A. Knuth c P.Z. Vördesive Vörding a J.D.P. Van Dijk a
J. Finet d A. Neumann c W. Longo d A. Bakhshandeh b C.L. Tiggelaar d
W. Gillis d H. Bailey d S.O. Peters b H.I. Robins d

aAcademic Medical Center, Amsterdam, The Netherlands; bMedical University of Lübeck, Lübeck,
cKrankenhaus Nordwest, Frankfurt, Germany; dUniversity of Wisconsin, Madison, Wisc., USA

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Whole-body hyperthermia · Sarcoma · Ifosfamide · Carboplatin

Abstract

Background: Based on earlier clinical and preclinical studies, we conducted a phase II trial in metastatic sarcoma patients of the combination of 41.8°C (×60 min) radiant heat (Aquatherm®) whole-body hyperthermia (WBH) with ‘ICE’ chemotherapy. The ICE regimen consists of ifosfamide (5 g/m²), carboplatin (300 mg/m²) and etoposide (100 mg/m²), concurrent with WBH, with etoposide also on days 2 and 3 post-WBH.

Methods: Therapy was delivered every 4 weeks for a maximum of 4 cycles. All patients received filgrastim or lenograstim.

Results: Of 108 patients enrolled as of September 2001, 95 are evaluable for response. Of the evaluable patients (mean ECOG performance status ~1; mean age 42.3; 58% male) 33 had no prior therapy for metastatic disease, and 62 were pretreated (mean: 1.5 prior regimens). The overall response rate was 28.4% (4 complete remissions and 23 partial remissions) with stable disease (SD) in 31 patients. For no prior therapy, the response rate was 36%; in pretreated patients it was 24%. The median overall survival by Kaplan-Meier estimates was 393 days (95% CI 327, 496); the median time to treatment failure was 123 days (95% CI 77, 164). The major toxicity (287 cycles) was grade 3 or 4 neutropenia and thrombocytopenia seen in 79.7 and 60.6% of treatments respectively; there were 7 episodes of infection (grade 3/4) with 2 treatment-related deaths, both involving disease progression and ureteral obstruction.

Conclusion: These results are consistent with continued clinical investigation of this combined modality approach.

Introduction

In spite of effective local regional therapy, 40–60% of patients with soft tissue sarcoma develop distant metastases and succumb to their disease. The role of chemotherapy for adult sarcoma patients has been extensively...
studied in both the metastatic and adjuvant/neoadjuvant settings. Adriamycin is the mainstay of therapy with response rates of 15–25% [1, 2]. Ifosfamide (IFO) has a similar response rate to Adriamycin both as first-line therapy and in Adriamycin-failing patients, although subset analysis suggests that the population of patients with leiomyosarcoma have been more resistant to IFO-based chemotherapy [1]. In phase III evaluation the use of combination chemotherapy in adults with high-grade sarcomas in comparison to Adriamycin as a single agent has been associated with increased toxicity but no improvement in survival [1–5].

Clearly, new innovative approaches to this group of neoplastic diseases are needed. Perfusional hyperthermia combined with chemotherapy and cytokines has successfully been employed for locoregionally advanced or recurrent tumor of the extremities, with the object of increased local control and limb-saving surgery [6–10]. Preclinical research in our laboratories has focused on hyperthermia enhancement of selected antineoplastic agents [11–19]. Some of these investigations have demonstrated an apparent improvement in therapeutic index (i.e., the relative ratio of neoplastic toxicity to normal tissue toxicity) [13, 16, 17, 20]. The biological basis for this hyperthermia effect may relate in part to inhibition of molecular mechanisms of chemotherapy resistance and induced increases in cellular drug penetration [13, 20–26]. Additionally, the biological sequelae of whole-body hyperthermia (WBH) including induction of cytokines [27–29], as well as the differential heating of bone marrow [30], can be exploited to optimize therapy.

A series of laboratory studies on carboplatin cytotoxicity and hyperthermia [14–16, 19, 20, 22] resulted in Robins et al. [31] conducting a phase I study of WBH and carboplatin (CBDCA). The experimental design of this clinical trial allowed for the comparison of the effects of WBH alone to CBDCA alone and to the combination of WBH and CBDCA for each patient. Consistent with preclinical modeling, this trial provided putative evidence that WBH does not change the pharmacokinetics of CBDCA with increased toxicity but no improvement in survival [1–5].

After these pilot phase I/II studies, supported by a strong biological rationale derived from the laboratory, it was decided to pursue a more definitive multi-institutional phase II study of ICE/WBH in order to define the response rate and survival in advanced sarcoma patients. In this paper the results of this clinical trial conducted by the Systemic Hyperthermia Oncology Working Group (SHOWG) [39] are reported.

### Materials and Methods

#### Patient Selection

One hundred and eight patients with histologically confirmed advanced-progressive soft tissue sarcoma not amenable to local treatment with curative intent or metastatic disease were entered on this trial at the Universities of Wisconsin, Amsterdam, Lübeck and Frankfurt between 5/1995 and 12/2000. It should be noted that the trial as originally conceived had a projected patient population not planned to exceed 40. The protocol was amended to expand the patient population in order to provide further data and insight into specific patient populations, i.e., pretreated vs. non-pretreated patients, and/or leiomyosarcoma vs. non-leiomyosarcoma patients. Inherent in this plan was the concept of obtaining data, which might serve as a foundation for the design of later clinical studies, e.g., phase III.

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 Universities of Wisconsin, Amsterdam, Frankfurt and Lübeck, and the Food and Drug Administration (USA).

Patients with and without prior therapy were eligible for study. Patients referred to each center had pathology review at that center, but there was no central pathology review. Patients were over 18.
1 Six patients were lost to follow-up. Seven patients received less than two courses of treatment, and were therefore not evaluable for response (2 patients secondary to toxicity (see Results)); 2 patients withdrew from study; 1 patient required surgery for an abdominal abscess; 2 patients who did not receive treatment (see Results: Toxicity). Three patients were under 18, but they all received only one treatment. VP-16 (Bristol-Meyers Squibb) at a dose of 100 mg/m² was given i.v. over 60 min, 10 min after achieving 41.8°C by esophageal temperature. VP-16 (Bristol-Meyers Squibb) at a dose of 100 mg/m² was given i.v. over 60 min, 10 min after achieving 41.8°C by esophageal temperature, as well as days 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% (1 g/m²) of the amount of IFO given per day.

Seven patients in this series received one cycle CBDCA at a slightly different time point (i.e., at the start of peak temperature, 41.8°C), versus 10 min later, as part of a toxicity optimization protocol, the results of which have been reported elsewhere [40].

Granulocyte Colony Stimulation Factor Administration. Granulocyte colony-stimulating factor (G-CSF) (filgrastim or lenograstim) was administered subcutaneously beginning 24 h after the last day of chemotherapy for at least 10 days. Patients with platelet counts <20 × 10⁹/l received platelet transfusions.

WBH Treatment Procedure and Supportive Care

The WBH treatment procedure is described in detail elsewhere [41]. A hyperthermia treatment session was defined as raising a patient’s systemic temperature (maximum temperature recorded by either rectal or esophageal probe, usually both) to 41.8 ± 0.2°C × 60 min. 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, the vapor barrier was removed to allow physiological temperature regulation.

The Aquatherm system for delivering WBH (patent, Cancer Research Institute, New York, N.Y., USA) has been previously described [36]. In brief, the apparatus produces radiant heat through circulating hot water in a cylinder constructed of copper tubing; the design incorporates a countercurrent distribution system to maintain thermal constancy. Other features include a humidification system to eliminate evaporative heat losses. Esophageal, rectal, skin and ambient air temperatures are monitored continuously and recorded at a minimum of 10-min intervals. Calibration and cleaning procedures have been detailed elsewhere [36, 41].

During all hyperthermia treatments, patients received nasal oxygen at 2–6 l/min. Patients received 0.75–1.0 l of i.v. 5% dextrose in 0.25 N saline per hour alternated with 5% dextrose in 0.5 N saline plus approximately 7.5 mEq of potassium chloride per liter. 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 lasts 4 h, including 1.3 h to reach target temperature, 1 h at 41.8°C, and a 1-hour cooling phase [41]. Post-treatment, patients received normal saline 500–1,000 ml as needed to maintain systolic blood pressures >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 ratio-

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Patients entered</th>
<th>108¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>63</td>
</tr>
<tr>
<td>Patients evaluable for response</td>
<td>95</td>
</tr>
<tr>
<td>Median ECOG performance status (range)</td>
<td>1 (0–2)</td>
</tr>
<tr>
<td>Mean age (range)</td>
<td>42.3 (16–64)</td>
</tr>
<tr>
<td>No prior chemotherapy</td>
<td>34 (36%)</td>
</tr>
<tr>
<td>Prior chemotherapy</td>
<td>61 (64%)</td>
</tr>
<tr>
<td>Mean number of regimens (range)</td>
<td>1.52 ((1–4)</td>
</tr>
<tr>
<td>Prior (epi)doxorubicin</td>
<td>51 (84% of pretreated patients)</td>
</tr>
<tr>
<td>Evaluable patients with leiomyosarcoma</td>
<td>26</td>
</tr>
</tbody>
</table>

¹ Six patients were lost to follow-up. Seven patients received less than two courses of treatment, and were therefore not evaluable for response (2 patients secondary to toxicity (see Results)); 2 patients withdrew from study; 1 patient required surgery for an abdominal abscess; 2 patients who did not receive treatment (see Results: Toxicity). Three patients were under 18, but they all received only one course or were lost to follow-up for various reasons, and have therefore not been included as a separate group.
nale for this have been previously described [41]. 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 >10 breaths/min.

During the procedure, heart rate, respiratory rate, oxygen saturation and cardiac rhythm were continuously monitored in all patients. Blood pressure (systolic/diastolic) was monitored at least every 10 min. Patients were observed after treatment for 20–24 h prior to discharge. After WBH, some patients received 10–35 mg of metoclopramide i.v. as prophylaxis against the gastric stasis effect of thiopental. Most patients received ondansetron or granisetron with dexamethasone for emetic prophylaxis.

**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 >3,000 cells/µl, an absolute granulocyte count ≥ 1,000 cells/µl and platelet count of ≥ 100,000 cells/µl. After cycle 2 of therapy, patients were evaluated for response. Responding or stable disease patients could receive up to 2 additional cycles of therapy unless there was evidence of progression. Patients with progressive disease were removed from study after 2 cycles. Patients were also removed from study in case of patient refusal, significant changes in the patient’s medical condition which would render the patient unacceptable for treatment in the judgment of the investigator, central nervous system disease while on study, or treatment delay for ≥ 4 weeks.

**Evaluation**

**Toxicity Evaluation.** Laboratory values, including blood counts and serum chemistries, were assessed at least weekly. Toxicity was assessed weekly and graded. At the conclusion of the study the Common Toxicity Criteria (CTC) (National Institute of Health – Version 2.0: http://ctep.info.nih.gov) were applied for final data analysis. All patients were considered evaluable for toxicity (n = 108).

**Response Evaluation and Statistical Considerations.** Patients were required to undergo at least two cycles of therapy to be evaluable for response (see table 1). Patients under the age of 18 were not used to evaluate the response rate as these patients were considered to be significantly more responsive to cytotoxic chemotherapy. After the second and fourth cycles, patients were evaluated for response based on standard criteria for objective regression of measurable lesions [42, 43], whether best measured by CT scans, other imaging studies or physical examination.

Traditional Kaplan-Meier plots were utilized to assess survival and time to progression. Analysis of response rate data was based on p values from the Fisher’s exact test for comparing two proportions.
Results

Patients

In this phase II study, 108 patients were included to receive a total of 278 treatment courses. All patients were evaluable for toxicity, and 95 patients were evaluable for response. Six patients were lost to follow-up after zero or one treatment cycle, and 7 patients received less than two courses of treatment for various reasons. Three patients were not evaluable for response because they were under

Table 2. Percent incidence\(^1\) of toxicity

<table>
<thead>
<tr>
<th>Toxicity grade</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>1.0</td>
<td>7.3</td>
<td>22.6</td>
<td>57.1</td>
</tr>
<tr>
<td>Infection</td>
<td>1.0</td>
<td>0.3</td>
<td>1.4</td>
<td>1.0</td>
</tr>
<tr>
<td>Platelet</td>
<td>2.7</td>
<td>11.5</td>
<td>16.7</td>
<td>43.9</td>
</tr>
<tr>
<td>Hb</td>
<td>14.9</td>
<td>28.6</td>
<td>8.7</td>
<td>5.9</td>
</tr>
<tr>
<td>GI</td>
<td>11.1</td>
<td>6.6</td>
<td>0.7</td>
<td>-</td>
</tr>
<tr>
<td>Nausea</td>
<td>6.0</td>
<td>3.8</td>
<td>2.0</td>
<td>-</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5.6</td>
<td>4.2</td>
<td>0.3</td>
<td>-</td>
</tr>
<tr>
<td>Hepatic</td>
<td>5.9</td>
<td>10.8</td>
<td>1.4</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.3</td>
<td>0.7</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Skin</td>
<td>0.3</td>
<td>0.3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Renal</td>
<td>3.5</td>
<td>0.7</td>
<td>0.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Pain</td>
<td>0.7</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^1\) 287 courses of treatment in 108 patients.


Toxicity

The main toxicity associated with WBH/ICE was myelosuppression, with grade 3–4 leukopenia in 79.7% of cycles, and grade 3–4 thrombopenia in 60.6% of cycles (table 2). Major bleeding episodes did not occur, and febrile neutropenia was rare. Generally speaking, patients became neutropenic and/or thrombocytopenic between days 7 and 10 of a treatment cycle. Patient counts typically recovered (i.e., < grade 2 toxicity) by day 14.

There were 2 deaths associated with ureteral obstruction, and sepsis. Both patients had ureteral obstruction before WBH, with a normal renal function. A third patient in whom ureteral stents were placed pre-therapy (to alleviate obstruction) also developed severe life-threatening urosepsis prior to becoming neutropenic. Although this patient survived her sepsis, and CT scans demonstrated significant disease improvement, it was elected not to proceed with further therapy in view of the perceived future risk. All 3 patients (treated at three different centers) were treated within weeks of one another, and in all 3 patients the sepsis occurred within 7 days of WBH/ICE treatment. Analysis of the experience resulted in excluding future patients with ureteral obstruction and/or ureteral stents from study entry.

In this high-screened patient population, that received lidocaine during WBH, we observed no cardiac complications.

Table 3. Efficacy in different patient cohorts

<table>
<thead>
<tr>
<th>Patient population</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n = 95)</td>
<td>4</td>
<td>23</td>
<td>31</td>
<td>37</td>
<td>28.4%</td>
<td>19.8, 38.5</td>
</tr>
<tr>
<td>No prior therapy (n = 34)</td>
<td>2</td>
<td>9</td>
<td>11</td>
<td>12</td>
<td>32.6%</td>
<td>19.6, 53.0</td>
</tr>
<tr>
<td>Prior therapy (n = 61)</td>
<td>2</td>
<td>14</td>
<td>20</td>
<td>25</td>
<td>26.2%</td>
<td>13.3, 35.1</td>
</tr>
<tr>
<td>Non-leiomyosarcoma (n = 69)</td>
<td>3</td>
<td>15</td>
<td>26</td>
<td>25</td>
<td>26%</td>
<td>15.6, 36.4</td>
</tr>
<tr>
<td>No prior therapy (n = 27)</td>
<td>2</td>
<td>6</td>
<td>10</td>
<td>9</td>
<td>29.6%</td>
<td>12.0, 47.2</td>
</tr>
<tr>
<td>Prior therapy (n = 42)</td>
<td>1</td>
<td>9</td>
<td>16</td>
<td>16</td>
<td>23.8%</td>
<td>12.0, 47.2</td>
</tr>
<tr>
<td>Leiomyosarcoma (n = 26)</td>
<td>1</td>
<td>8</td>
<td>5</td>
<td>12</td>
<td>31%</td>
<td>12.9, 49.1</td>
</tr>
<tr>
<td>No prior therapy (n = 7)</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>42.9%</td>
<td>5.5, 80.3</td>
</tr>
<tr>
<td>Prior therapy (n = 19)</td>
<td>1</td>
<td>5</td>
<td>4</td>
<td>9</td>
<td>31.6%</td>
<td>10.3, 52.9</td>
</tr>
</tbody>
</table>

\(n = \) Number of patients; RR = % response rate (PR + CR); CI = confidence interval; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.
Specific WBH-associated toxicities consisted of redness or grade I blisters on pressure spots in less than 5% of patients, and on the leg of a patient with a previous deep venous thrombosis in that limb (before start protocol). Both redness and blisters healed in days, without sequelae, and no treatment was withheld because of them. One patient in the series developed paradoxical excitation with the sedation protocol, and could not be treated. It was subsequently discovered the patient had a previous history of a similar event post-operatively. (Our group had not observed this phenomenon in any of the previous studies.) A second patient had an inappropriate blood pressure response (i.e., hypotension) at the start of WBH and was not treated.

**Efficacy**

In our population, the overall response rate was 29.2%, with 4 complete responses and 23 partial remissions in 95 evaluable patients. The response rates were higher for untreated patients (36.3 vs. 24.2%), as was to be expected, although this was not statistically significant ($p = 0.238$). Leiomyosarcoma patients did not do worse in this study than patients with other histologies ($p = 0.796$), even after prior treatment ($p = 0.543$). Table 3 lists responses and analysis by histological type and prior treatment.

Of the 16 responding patients (in this study) who were refractory to prior therapy, only 2 patients received single agents: doxorubicin; high-dose IFO with stem cell rescue. Of the 14 patients who had failed combination therapy, all had been treated with at least one of the drugs contained in the ICE regimen (among them 10 patients with IFO). For the entire evaluable patient cohort the median Kaplan-Meier estimates for survival was 327 days with a 95% confidence interval (CI) of 393, 496. The median time to treatment failure (TTF) by the same method was 123 days with a 95% CI of 77, 164 (fig. 2, 3). Kaplan-Meier curve of survival probability (solid line) with 95% CI (dashed lines) for the evaluable patient cohort ($n = 95$). The median survival estimate is 393 days (CI 327,496). Of the 95 evaluable patients 62 had died by the end of follow-up.
Meier estimates comparing responding patients to patients with stable disease (SD) and disease progression (PD) showed increased overall survival for responding patients (529 days (393, 690)) versus patients with SD (448 days (298, \(\infty\)) or PD (274 days (184, 416)). Based on the log rank test, the difference in survival for responders versus PD was statistically significant (\(p = 0.04\)), as was that for SD versus PD (\(p = 0.07\)). There was no statistically significant difference in TTF for responding patients versus patients with SD (215 vs. 188 days, \(p = 0.31\)).

**Discussion**

The rationale for WBH in combination with chemotherapy as a treatment for advanced cancer, based on extensive preclinical studies, has been strong for decades [reviewed in 24]. However, the toxicity associated with extracorporeal WBH has until recently precluded the conduct of larger, multi-institutional studies of WBH [32, 33]. The use of a radiant heat WBH device has eliminated that excessive toxicity [36]. The toxicity and efficacy of ICE chemotherapy concurrent with WBH was studied in patients with advanced soft tissue sarcomas (ASTS).

In this study, 108 patients with ASTS were treated in four institutions in three countries. WBH was combined with the three-drug combination regimen ICE, which has shown response rates of around 20% in a large series of heavily pretreated cancer patients with a variety of tumors [34]. In addition, all three drugs incorporated in the regimen show thermal enhancement [12–16, 19, 20, 35]. ICE causes considerable hematological toxicity, with febrile neutropenia, and frequent need for platelet and red blood cell transfusion. In the 278 treatment courses in the presented patient group, toxicity was substantial, albeit comparable to that seen in ICE without WBH. Fatal or
near-fatal toxicity was seen in 3 patients with ureteral obstruction due to tumor. Although myelosuppression necessitated red blood cell and/or platelet transfusions in the majority of patients, the predictability of this side effect made management fairly easy. This is illustrated by the lack of major bleeding complications, even though over 60% of cycles were associated with grade 3–4 thrombocytopenia. The preemptive 10-day administration of G-CSF may have contributed to the low incidence of neutropenic fever and serious infections. The biological basis for the lack of increase in hematological toxicity of ICE and WBH versus ICE without WBH, in spite of hyperthermia’s demonstrated ability to enhance cytotoxicity, relates in part to the induction of cytokines [27–29]. The timing of chemotherapy in relation to the time course of WBH may further explain this phenomenon [30, 40].

The absence of specific serious WBH-associated toxicity is probably related to the radiant heat technology of the WBH device, and the fact that it does not require intubation anesthesiology or vasopressor support.

Over the last two decades, over 1,700 patients with ASTS have been treated in the context of phase III clinical trials. Such studies have failed to demonstrate a survival advantage for multidrug regimens over single-agent doxorubicin, or for any particular drug combination regimen over any other [4, 5, 44, 45]. Response rates in these studies are generally around 20–25% for chemotherapy-naive patients. Although some studies showed superior response rates with combination therapy, this did not confer a survival benefit in any randomized trial [1, 4, 5, 44–48]. In all studies, chemotherapy-pretreated patients have even worse outcomes.

In our cohort of 95 evaluable patients, a 29.2% overall response rate was observed. Clearly this response rate and the observed overall survival are consistent with those seen in prior cooperative group trials involving untreated patients. Data on the results of ICE in sarcoma patients are not available, since the only previous experience with ICE chemotherapy in ASTS involved 10 refractory patients, in whom 2 responses were observed [34]. In the present patient group, the majority of patients had been pretreated, and though their response rate was lower than that in non-pretreated patients (36.3 vs. 24.2%) this difference did not reach statistical significance. The majority of the pretreated patients that achieved a response had been pretreated with both Adriamycin and IFO, the two most active drugs in this disease.

In focusing on the observed results in pretreated patients (having received various components of the ICE regimen), it is tempting to speculate that WBH may serve to overcome chemotherapy resistance. The biological basis for this speculation relates to preclinical and clinical studies showing WBH inhibition of NAD+ synthesis, as NAD+ is the rate-limiting substrate for the DNA repair enzyme poly(ADP-ribose) polymerase [23]. More recent laboratory data (described in the Introduction above) demonstrated the ability of hyperthermia to overcome intrinsic VP-16 resistance [35].

Outcome in sarcoma patients is to a certain degree dependent on histological subtype, which starts with the distinction between bone sarcomas and soft tissue sarcomas. Within the soft tissue sarcomas, the main subtypes that confer a different prognosis and therefore lead to different treatment strategies, are those of the small round blue cell sarcomas (such as extra-osseous Ewing sarcoma or PNET) and the leiomyosarcomas/gastrointestinal stromal tumors (GIST). While the former are considered to be neuroendocrine tumors especially sensitive to systemic treatment, the latter are typically considered to be chemotherapy-resistant. In randomized studies of chemotherapy for advanced soft tissue sarcomas, treatment typically yields response rates of around 25%, with response rates in leiomyosarcomas of only 10–15% [1, 4]. Only recently, molecular studies have identified the specific tyrosine kinase defect in GIST, that distinguishes it from leiomyosarcoma [49]. CD117 immunohistochemistry of the tumor is now routinely performed to establish the differential diagnosis [50], but this was not yet the case when the present study was undertaken.

In this study, no patients with bone sarcomas or small round blue cell tumors were included, but the analysis was broken down into leiomyosarcoma and non-leiomyosarcoma patients. Stratification for other histological subtypes was not part of the analysis. In most studies further histological subtyping has failed to be associated consistently with distinct clinical behavior or response to therapy. Even the classical association of synovial sarcoma with high response rate to IFO was based on treatment of 8 patients in a randomized trial [5], which could not be confirmed in later studies [1]. The small size of all subgroups except leiomyosarcomas renders comparison even more tenuous.

The 31% response rate in the 26 leiomyosarcoma patients (3 in 7 chemotherapy-naive patients, and 6 in 19 pretreated patients) is a relatively good result, and hints that this population may uniquely benefit from the WBH/ICE combination, particularly as a salvage therapy.

In this patient cohort, responding patients survived significantly longer than non-responders, and the difference was 81 days. Although intuitively it is to be expected

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that responding patients have superior outcomes (since responses tend to reflect biological behavior at least as much as treatment effect), in many sarcoma studies improved response rates did not lead to increased survival for the treated group [1, 4, 5, 44–48]. The fact that in this series, with its large proportion of pretreated patients, responses were associated with increased survival is reassuring.

The study is limited in several ways. The ICE regimen is not a standard treatment for ASTS, and comparison even with historical data in sarcoma patients is impossible. Also, IFO is the most active drug of the regimen in sarcoma, and it is unclear what the results of WBH and IFO single agent might be. The contribution of the other drugs is less certain, even though thermal enhancement has been proven preclinically, and each drug shows at least some single-agent activity in ASTS [2]. In the ICE regimen, CBDCA was dosed by mg/m² rather than by AUC, as is the standard nowadays. The heterogeneity in renal function even among individuals with ‘normal’ creatinine levels might generate different exposure to the drug, which may lead to both underdosing with loss of efficacy, and overdosing with increased toxicity. It is conceivable that the considerable thrombocytopenia seen with the ICE regimen partly relates to carboplatin overdosing.

The interpretation of response and survival data is more difficult in phase II versus randomized trials, mainly due to the selection bias introduced by the trial design. The latter holds especially true for the fairly extensive cardiopulmonary screening that was part of the pretreatment procedure in WBH. The data collected did not include quality or duration of response to prior therapy, although these data might have supported the hypothesis about reversal of resistance to chemotherapy by WBH.

In summary, this clinical trial demonstrates the feasibility of performing a large multicenter cooperative group study involving WBH. Our findings, as well as the preclinical studies and earlier clinical investigation taken collectively, support the continued investigation of this multimodality approach in this poor-prognosis patient population. The results obtained were particularly encouraging relative to patients with leiomyosarcoma. We propose that the outcome of this study provides a strong foundation for a phase III randomized clinical trial of chemotherapy with and without WBH in ASTS.

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