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Systemic chemotherapy using paclitaxel and carboplatin plus regional hyperthermia and hyperbaric oxygen treatment for non-small cell lung cancer with multiple pulmonary metastases: Preliminary results

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Abstract

Purpose: The purpose of this retrospective case series was to evaluate the toxicity and efficacy of systemic chemotherapy using paclitaxel and carboplatin plus regional hyperthermia (HT) and hyperbaric oxygen treatment (HBO) for non-small-cell lung cancer (NSCLC).

Materials and methods: Twenty-two patients with NSCLC with multiple pulmonary metastases intravenously received paclitaxel (50 mg/m^2), carboplatin (area under the curve of 1.0–1.5) and 10% glucose weekly for 3 out of 4 weeks. Hyperthermia (HT) of the whole thoracic region was also administered weekly during intravenous infusion of carboplatin in all patients. In addition, 16 (72%) of 22 patients received hyperbaric oxygen (HBO) treatment immediately after weekly chemotherapy. A total of 107 cycles were performed in 16 patients with HBO, and 27 cycles in 6 patients without HBO. The toxicity and efficacy of these patients were retrospectively analyzed.

Results: Both the hematologic and non-hematologic toxicities were mild and leucopenia/neutropenia of $\geqq$ grade 3 was seen in one patient, while pneumonitis of $\geqq$ grade 3 occurred in one patient. Fourteen (64%) of 22 patients had an objective response. The median time to progression of disease in all patients was 8 months and in 16 patients with HBO was 9 months. Four (44%) of 9 patients with prior chemotherapy including paclitaxel and carboplatin obtained objective responses.

Conclusions: The novel combined therapy of paclitaxel and carboplatin with HT and HBO may therefore be a feasible and promising modality for treating NSCLC with multiple pulmonary metastases, and the results justify further evaluation to clarify the benefits of this treatment regimen.

Keywords: *Hyperthermia, chemotherapy, hyperbaric oxygen, non-small-cell lung cancer*

Introduction

Lung cancer is currently the most common cause of cancer deaths in many countries, including Japan. Although meta-analyses have proved that cisplatin-based chemotherapy improves survival compared with the best supportive care, the benefits have been modest [1]. During the past several years, some new chemotherapeutic drugs with novel mechanisms of action, including paclitaxel, have demonstrated a promising activity in patients with advanced non-small-cell lung cancer (NSCLC). In the USA, the combination of paclitaxel and carboplatin has been a widely used regimen for NSCLC because of its low toxicity profile and efficacy [2].

The rationale for the use of hyperthermia (HT) as a treatment for cancer rests on several mechanisms [3, 4]. HT is known to cause direct cytotoxicity, while it also acts as a radiation-sensitizer and chemo-sensitizer. Although the combination of HT with

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radiation has been the focus of more attention, there is an equally strong rationale for combining HT with chemotherapy. The mechanisms of action have been considered to be as follows: HT increases drug uptake into cells, increases oxygen radical production, increases DNA damage and inhibits DNA repair [3]. Many chemotherapeutic agents exhibit synergism with HT [3–8]. As for carboplatin, several previous in vitro/vivo studies showed synergism with HT at 40 to 44°C [5, 6]. The optimal sequence between the application of heat and drug administration is to administer them simultaneously or to give the drug immediately before the onset of heating [5, 6]. For paclitaxel, several in vitro/vivo studies also showed synergism with HT [7, 8], while other studies failed to show a significant thermal enhancement of paclitaxel cytotoxicity [9, 10]. Despite the results of studies demonstrating the efficacy of chemotherapy with HT, the utilization of this combination in clinical practice is still limited. Recently, Zoul et al. showed the treatment results of weekly paclitaxel combined with local HT in patients with recurrent breast cancer; an objective local response was observed in all treated patients (complete response in 4 patients and partial response in 3) [11]. In the patients with a pleural dissemination of NSCLC, the treatment results of post-operative HT combined with the intra-thoracic administration of cisplatin have been reported; the overall survival of the treated group ($n = 24$) was significantly prolonged in comparison to a historical control group treated by either surgery alone ($n = 17$) or exploratory thoracotomy ($n = 11$) [12]. However, there are no clinical reports of systemic chemotherapy using paclitaxel and carboplatin combined with regional HT for NSCLC.

Several researchers have combined hyperbaric oxygen treatment (HBO) with chemotherapy to enhance drug cytotoxicity for cancer [13–17]. Many human solid tumors are composed of regions that are well vascularized and normoxic, while other regions are relatively hypoxic. Hypoxic cells in the malignant tumor are relatively more resistant to chemotherapy. The increase in oxygen partial pressure in hypoxic populations may explain the increase in the anti-tumor effect of these chemical agents. In animal cancer models, several studies that previously combined HBO with various chemotherapeutic agents have shown increases in the mean survival times and/or decrease in tumor growth [13–15]. In limited clinical studies, the combination of HBO and chemotherapy showed a potential value of increased survival for advanced cancer and the side effects did not increase by combining HBO with chemotherapy [16, 17].

In this context, a novel combined therapy of systemic chemotherapy using paclitaxel and carboplatin plus regional HT and HBO was administered to improve the clinical outcomes in NSCLC. The combined therapy for NSCLC with multiple pulmonary metastases was started in 2003. The main purpose of our study was to evaluate the toxicity and efficacy of this combined therapy in patients with NSCLC.

Materials and methods

Data collection

Data were collected from patient medical records for this retrospective case series. This study focused on data obtained from 52 NSCLC patients who received systemic chemotherapy with regional HT at two hospitals in Japan. The patients were included in the study if they were eligible to receive systemic chemotherapy using paclitaxel and carboplatin plus regional HT with or without HBO for NSCLC with multiple lung metastases. Thirty patients with extrathoracic metastases, except for brain metastases, were excluded from this study; because the heating electrodes of regional HT did not cover those metastases and there were considerable un-heated or inadequately heated lesions in those cases we considered that the patients were not suitable for this case series. We included ten patients with brain metastases, since all the metastatic lesions of the brain were able to be treated with stereotactic radiosurgery, which provides higher local control rates regardless of whether or not chemo-hyperthermia is performed. In addition, any patients who had radiotherapy of the thoracic region added to the combined therapeutic regimen were also eliminated.

Patients

Twenty-two patients (13 men and 9 women, age range, 47–77 years; median, 66 years) were chosen from the data base using the inclusion and exclusion criteria mentioned above. Sixteen of the 22 patients also received HBO therapy at one hospital, since the remaining 6 patients were treated at the other hospital where a hyperbaric chamber was not available. Between September 2003 and September 2007, all 22 patients were placed on the above described regimen. The patients were selected for this treatment by the following criteria: histologic or cytologic proof of NSCLC; age between 18 and 80 years; Eastern Cooperative Oncology Group (ECOG) performance status 0–2; absolute neutrophil count $\geqq 3{,}000/mm^3$ and platelet count $\geqq 100{,}000/mm^3$; serum bilirubin, ALT, AST, ALP, urea, and creatinine levels within normal limits. The patient characteristics are given in Table I. The ECOG performance status and site of the disease

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Table I. Patient characteristics.

Characteristics	$N = 22$
Median age, years (range)	66 (47–77)
Gender, male/female	13/9
Performance status, 0/1/2	0/10/12
Histology	
Adenocarcinoma	20
Large cell carcinoma	2
Sites of disease	
Lung	22
Pleural effusion	1
Lymph nodes	
Mediastinal	10
Supraclavicular	1
Brain	10
Prior surgery for primary	4
Prior RT for primary	10
Prior chemotherapy	14
Cisplatin	2
Carboplatin	11
Gemcitabine	6
Paclitaxel	9
Vinorelbine	5
Gefitinib	4
HBO	16
SRT for brain metastasis	10

RT, radiotherapy; HBO, hyperbaric oxygen treatment; SRT, stereotactic radiosurgery.

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were evaluated at the start of treatment. There were 10 cases with brain metastases. Fourteen patients (64%) had prior chemotherapy, of which 9 patients (41%) had undergone paclitaxel and carboplatin. Ten patients (45%) had received prior RT for primary lesions. Four patients had postoperative recurrence. Ten (45%) of 22 patients underwent stereotactic radiosurgery for brain metastasis. Written informed consent for treatment was obtained from all patients.

Chemotherapy

The treatment cycle was 4 weeks long. The chemotherapy was administered weekly for 3 weeks followed by 1 week of rest. Paclitaxel (Taxol, Bristol-Myers Squibb, Princeton, NJ; 50 mg/m^2) was given intravenously over 1 hour, followed by carboplatin (Paraplatin, Bristol-Myers Squibb; area under the curve (AUC) of 1.0–1.5, depending on the age, clinical status and bone marrow tolerance) by intravenous infusion over 1 hour. The carboplatin dose was calculated by using a Calvert formula with creatinine clearance substituted for the glomerular filtration rate [18]. The patients received premedication consisting of 10% glucose which was administered to further increase the value of thermochemotherapy by lowering the tumor pH [19], 4–8 mg dexamethasone intravenously, 3 mg granisetron hydrochloride intravenously, 50 mg diphenhydramine hydrochloride orally, and 50 mg ranitidine intravenously.

There were no patients who required a dose reduction of chemotherapy. The treatment was delayed in 7 (5%) cycles. All patients could be treated on an outpatient basis. A total of 107 cycles were performed in 16 patients with HBO, and 29 cycles in 6 patients without HBO. The median number of cycles in the patients with HBO was 7 (range 1–13) while in the patients without HBO it was 4 (range, 3–8).

The chemotherapy with paclitaxel and carboplatin was performed as an initial chemotherapy in 8 patients (36%), as a second-line in 8 (36%), as a third-line in 3 (14%) and as a fourth or sixth-line in 3 (14%). Any drugs administered as prior chemotherapy were listed in Table I.

Hyperthermia

HT was performed during every intravenous infusion of carboplatin for all cycles of chemotherapy. The heating duration ranged from 40–60 min. The heat was applied using 8-MHz radiofrequency-capacitive regional HT (Thermotron RF-8, Yamamoto Vinita Co., Osaka, Japan). The physical features of the RF-8 clinical HT machine and thermal distribution characteristics in a phantom as well as in the human body when heating with this device have all been reported previously [20, 21]. In all cases, both the upper and the lower electrodes measured 30 cm in diameter, and they were placed on opposite sides of the entire thoracic region. The treatment posture for all cases was the prone position. The patients were instructed carefully to mention any unpleasant sensations suggestive of a hot spot. The RF-output increased to the maximum level tolerated by the patients after any unpleasant sensations either vanished or decreased to a fully sustainable level by superficial cooling and/or fine adjustments of the body position. For superficial cooling to reduce the preferential heating of the subcutaneous fat tissue, overlay boluses were applied in addition to regular boluses which were attached in front of the metal electrodes. Some previous studies showed a strong positive correlation to exist between the RF-output and temperature of tumors in this device [22, 23]. Because the measurement of direct intra-tumor temperature was clinically difficult, invasive or distressing, previous correlative data between RF-output and intra-esophageal temperature at the above setting of the whole thoracic HT in a large number of patients was used to estimate the heating temperature: $Y = 0.0056X + 36.6$, $X =$ median RF-output (W); $Y =$ maximum intra-esophageal temperature (°C) [23].

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Table II. Toxicity* in all the patients.

	Grade 0 (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Leucopenia	6 (27)	11 (50)	4 (18)	1 (5)	0
Neutropenia	6 (27)	10 (45)	5 (23)	1 (5)	0
Anemia	17 (77)	4 (18)	1 (5)	0	0
Thrombocytopenia	21 (96)	1 (5)	0	0	0
Neuropathy	20 (90)	1 (5)	1 (5)	0	0
Pneumonitis	20 (90)	1 (5)	0	1 (5)	0
Diarrhea	22 (100)	0	0	0	0
Nausea	21 (95)	1 (5)	0	0	0
Vomiting	21 (95)	1 (5)	0	0	0
Hypersensitivity reaction	21 (95)	0	1 (5)	0	0
Renal toxic effect	22 (100)	0	0	0	0
Cardiac toxic effect	22 (100)	0	0	0	0
Fatigue	12 (55)	8 (36)	2 (9)	0	0

*The National Cancer Institute Common Toxicity Criteria version 3.

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The median RF-output in all patients ranged from 800 to 1600 W (median 1,250 W). The median maximum intra-esophageal temperature in all the patients was calculated to be 43.6°C (range, 41.1–45.6°C) from the correlative data between the median RF-output and intra-esophageal temperature.

Hyperbaric oxygen therapy

HBO was performed as a chemotherapy adjuvant to increase tumor sensitivity to anticancer agents immediately after weekly chemotherapy and regional HT for all cycles. The patients underwent a single treatment for 60–90 minutes in a monoplace HBO chamber (Sechrist Industries Inc., model 2800 J, Anaheim, California) pressured with 100% oxygen to 2.0 atmospheres absolute.

Evaluation of the toxicity and efficacy

The National Cancer Institute Common Toxicity Criteria version 3 was used to score toxicity. The highest toxicity grade for each patient in all cycles of this therapy was used for the toxicity analysis.

The primary endpoints of this study regarding efficacy were the objective response rate and the time to progression of disease (PoD). The patients were evaluated every 4 weeks (after the completion of one cycle) by computed tomography (CT) scanning for measurable lesions. The objective response was evaluated according to the World Health Organization criteria [24]. A complete response (CR) was defined as the complete disappearance of all clinically detectable tumors for at least 4 weeks. A partial response (PR) required at least a 50% reduction in the sum of the products of the longest perpendicular diameters of all measurable lesions. Progressive disease (PD) required a 25% increase in measurable lesions or the appearance of any new measurable or non-measurable lesion. Any patients who did not meet the definitions of response or progression were classified as having no change (NC). The time to PoD was calculated from the first day of the combined therapy of this study to the date of disease progression. The overall and disease progression-free survival rates were calculated from the start of the combined therapy by the Kaplan-Meier method.

Results

The follow-up from the start of the combined treatment ranged from 6 to 32 months (median, 16). The degrees of toxicity are listed in Table II. Both hematologic and non-hematologic toxicities were mild. For the toxicities of $\geqq$ grade 3, leucopenia/neutropenia of grade 3 was seen in only one patient, and pneumonitis of grade 3 occurred in one patient. For these toxicities, there were no clear differences between those who did and did not receive HBO. Generally, HT was well tolerated by the patients, and only the initial contact with the cold boluses caused some discomfort, which thereafter rapidly dissipated. No patients experienced any thermal burns. The weekly HBO treatment was also well tolerated. Although some patients experienced hearing difficulties either during or shortly after HBO, no serious or life-threatening complications with HBO were observed.

Table III lists all patients associated with the treatment parameters and results. Fourteen (64%) of 22 patients had an objective response (4 CRs, 10 PRs). Twelve (75%) of 16 patients with HBO and 2 (33%) of 6 patients without HBO had an objective response. The time to PoD was 2 to 18 months (median, 8 months). Figure 1 shows the progression-free survival rates in all patients. The median time to

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Table III. Treatment results in all the patients.

Case	Stage*	Line of CT	Prior CT including PC	Prior platinum based CT	Median RF output**	Median heating time	No. of cycles	HBO	Tumor response	Time to POD (mos)
1	IV	1st	–	–	1300	50	8	Yes	CR	12
2	IV	1st	–	–	1500	50	7	Yes	CR	10
3	IV	1st	–	–	1600	50	6	Yes	CR	5
4	IV	1st	–	–	1500	50	13	Yes	PR	13
5	IV	1st	–	–	1500	50	3	Yes	NC	4
6	IV	1st	–	–	1100	40	3	Yes	NC	4
7	IV	2nd	No	No	1200	50	10	Yes	PR	13
8	IV	2nd	No	Yes	1200	50	5	Yes	PR	6
9	IV	2nd	No	No	1500	50	8	Yes	PR	8
10	IV	2nd	No	Yes	1350	50	11	Yes	PR	9
11	IV	2nd	Yes	Yes	1000	40	1	Yes	PD	2
12	IV	3rd	No	No	1500	50	7	Yes	PR	17
13	IV	3rd	Yes	Yes	1300	40	4	Yes	PR	18
14	IV	4th	Yes	Yes	1500	50	3	Yes	NC	4
15	IV	4th	Yes	Yes	1200	50	10	Yes	PR	8
16	IV	6th	Yes	Yes	800	50	8	Yes	CR	18
17	IV	1st	–	–	800	50	6	Yes	PR	8
18	IV	1st	–	–	800	50	8	Yes	NC	10
19	IV	2nd	Yes	Yes	1000	50	4	Yes	PR	4
20	IV	2nd	Yes	Yes	800	40	4	Yes	NC	4
21	IV	2nd	Yes	Yes	1000	50	3	Yes	NC	3
22	IV	3rd	Yes	Yes	1500	50	4	Yes	NC	4

*TMN classification of malignant tumors (UICC). 6th ed.
**Mean maximum radiofrequency output power
CT, chemotherapy; PC, paclitaxel and carbopatin; RF, radiofrequency; HBO, hyperbaric oxygen; POD, progression of disease; mos, months; CR, complete response; PR, partial response; NC, no change.

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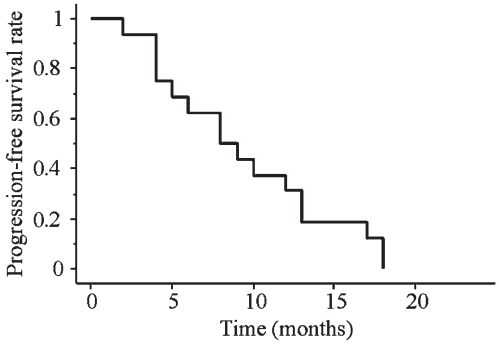

Figure 1. The progression-free survival rate.

PoD in the patients with HBO was 9 months and without HBO was 4 months. Of the 14 patients who had prior chemotherapy, 9 (64%) patients achieved an objective response (1 CR, 8 PRs). In addition, of the 9 patients with prior chemotherapy including paclitaxel and carboplatin, 1 patient obtained a CR and 3 patients a PR. The median overall survival time of all patients was 17 months.

Discussion

The present study is the first study trying to assess a combination therapy of systemic chemotherapy using paclitaxel and carboplatin with regional HT and HBO in patients with NSCLC. As for regional HT-related toxicity, subcutaneous fat burns were observed in 3–12% of patients, but generally, these healed spontaneously and did not result in a discontinuation of the treatment [25, 26]. The previous phase II trials of systemic chemotherapy with regional HT demonstrated that HT did not adversely influence the tolerability of the chemotherapeutic drugs, even when given at maximum tolerated single modality doses [27, 28]. In the current study, weekly regional HT and HBO treatment were well tolerated and $\geqq$ grade 3 hematologic or non-hematologic toxicities were recognized in only 1 (5%) patient; the novel combined therapy of paclitaxel and carboplatin with HT and HBO may therefore be a feasible treatment modality. It seems that regional HT also did not reveal any significant increase in the toxicity from either chemotherapy or HBO in our combined therapy.

An interesting result in this study was that the reintroduction of paclitaxel and carboplatin caused an objective response in 4 (44%) of 9 patients who had already received chemotherapy using paclitaxel and carboplatin. Experimental reports have shown that use of HT with many chemotherapeutic drugs had the potential ability to reverse the drug resistance, although the mechanisms underlying

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the reversal of drug resistance are not well defined [3]. Westermann et al. conducted whole body HT with carboplatin for the patients with platinum-resistant ovarian cancer and a tumor response was observed in 5 of 12 patients [29]. These observations suggest that further investigations of the therapeutic potential of HT with or without HBO in a group of patients who historically fail to respond to chemotherapy alone is thus warranted.

In our study, regional HT and HBO were administered concurrently with a weekly decreased application of paclitaxel (50 mg/m^2) and carboplatin (AUC of 1.0–1.5). The regimen of carboplatin every 3 weeks and weekly paclitaxel chemotherapy has been suggested to be the most effective and least toxic treatment for advanced NSCLC [30]. Regarding the management of several other tumors, however, weekly regimens of paclitaxel and carboplatin have shown increased efficacy and decreased toxicity [31, 32]. Recently, a phase II study of weekly paclitaxel (100 mg/m^2) and carboplatin (AUC of 2.0) for advanced NSCLC appeared to be less toxic than the standard 3-week regimen of either a similar or smaller dose intensity, and also showed comparable clinical outcomes; namely, response rate was 44%, and the time to PoD was median 5 months [33]. The other phase II study for the decreased dose of weekly paclitaxel (50 mg/m^2) and carboplatin (AUC of 2.0) for elderly patients ($\geq$65 years of age) with NSCLC, the toxicities were mild; however, the objective response rate was only 14%, and the time to PoD was median 4 months [34]. Several large phase III studies for chemotherapy alone using the combination of paclitaxel and carboplatin for NSCLC have reported a response rate of 17–32% and median time to PoD of 3–7 months [30, 35–37]. Although the comparison of our retrospective small series with the prospective trials is not valid, a response rate of 75% and median time to PoD of 9 months was obtained for stage IV cases in spite of the mild toxicities with our therapy using a low dose level of paclitaxel and carboplatin with regional HT and HBO. In contrast, all aforementioned phase II and III studies included not only stage IV but also IIIB. In previous clinical results to identify prognostic factor for the patients with advanced NSCLC treated with carboplatin and paclitaxel, only disease stage of IV (IIIB versus IV) was a significantly worse prognostic factor on progression-free survival [38]. Therefore, both HT and HBO might be potentially valuable due to their actions as chemo-sensitizers.

HBO has been investigated as a radio-sensitizer. Many investigators showed that HBO improved tumor oxygenation, and treatment with HBO during or immediately after RT has been shown to improve the radiation response in solid tumors [14]. Hypoxic cells in the malignant tumor are relatively more resistant to ionizing radiation than normoxic portions within the same tumor. Since hypoxic cells in the malignant tumor are also relatively more resistant to chemotherapy, HBO could increase the anti-tumor effect of chemical agents. Several researchers have combined HBO with chemotherapy to enhance drug cytotoxicity [13–17, 39]. A human prostatic carcinoma cell line grown under normoxic conditions was exposed to paclitaxel for 90 minutes under HBO or normal pressure air, and HBO increased the sensitivity of cells to paclitaxel [39]. In a bulky hypoxic tumor such as epithelial ovarian cancer, dramatic tumor neovascularization was found in tumors of mice exposed to HBO, and there was significant tumor growth retardation in the mice receiving both cisplatin and HBO in comparison to those treated with cisplatin alone [13].

On the other hand, previous results of HT at mild temperatures of 39–42°C also demonstrated an improvement in tumor oxygenation in human tumors [40]. Therefore, the combination of HBO and HT in these clinical results might strongly increase the tumor oxygenation and contribute to the favorable outcomes. To our knowledge, no in-vitro/vivo study has ever been reported on the combination of HBO and HT to improve the antitumor efficacy of chemotherapy. Further evaluations of the details of this combined treatment protocol, such as the timing, dose of chemotherapy, atmosphere and heating temperature, using both experimental analyses and prospective clinical trials in a large number of patients, are thus needed to confirm the clear benefits of this regimen.

Promising results have been reported regarding RT plus regional HT using RF-8 for lung cancers [41, 42], however, the disadvantages of an RF-capacitive device for the preferential heating of the subcutaneous fat tissue are well known, while Asian patients are considered to be relatively suitable due to their slender constitution. The excessive power deposition in the fatty tissue limits the effectiveness of the capacitive technique. In the current study, although direct tumor thermometry was not employed, that tumor temperature in most of our patients might reach, at least, 39–42°C, which demonstrated an improvement in tumor oxygenation, because $\geq$41.1°C of the maximum intraesophageal temperature was estimated in all the patients.

There are several limitations in this study. First, because this study was a retrospective case series report; the patients' characteristics, such as the degree of pretreated chemotherapy and whether or not they had brain metastases, were variable and might have influenced the results. A formal

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phase II trial is consequently needed to determine the efficacy for this combined therapy in the patients with advanced NSCLC. Second, this study could not assess the additional value of HBO to chemo-hyperthermia, since a proper control group was not included; only six patients were treated without HBO.

In summary, this is the first report attempting to assess the toxicity and efficacy of systemic chemotherapy using paclitaxel and carboplatin plus regional HT and HBO in patients with NSCLC. Based on this small retrospective series, this combined therapy thus appears to be a feasible treatment modality and therefore warrants further investigation in regard to the effective treatment of NSCLC with multiple pulmonary metastases.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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