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Feasibility study of metabolically supported chemotherapy with weekly carboplatin/paclitaxel combined with ketogenic diet, hyperthermia and hyperbaric oxygen therapy in metastatic non-small cell lung cancer

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ABSTRACT

Background: Previous evidence suggests that metabolically supported chemotherapy (MSCT), ketogenic diet, hyperthermia and hyperbaric oxygen therapy (HBOT) could all target vulnerabilities of cancer cells. This study aimed to evaluate the efficacy and the tolerability of this combination therapy in the treatment of stage IV non-small cell lung cancer (NSCLC).

Methods: Forty-four NSCLC patients with distant metastasis that received MSCT (administration of chemotherapy regimen following induced hypoglycemia) plus ketogenic diet, hyperthermia and HBOT combination were included in this retrospective study. Survival and treatment response rates as well as toxicities were evaluated.

Results: Overall response rate (ORR, complete response plus partial response) was 61.4%; whereas, 15.9% and 22.7% of patients had stable disease (SD) and progressive disease (PD), respectively. Mean overall survival (OS) and progression-free survival (PFS) was 42.9 months (95% CI: 34.0–51.8) and 41.0 months (95% CI: 31.1–50.9), respectively. A higher Eastern Cooperative Oncology Group (ECOG) performance status (ECOG ≥2) was associated with worse OS and PFS. Patients received chemotherapy cycles with acceptable toxicity and adverse events. No problems were encountered due to fasting, hypoglycemia, ketogenic diet, hyperthermia or hyperbaric oxygen therapy.

Conclusions: Findings of this study suggest that MSCT combined with other modalities targeting multiple pathways and cellular vulnerabilities may bring about remarkable improvements in survival outcomes and treatment response rates in metastatic NSCLC, without additional safety concerns. Large comparative studies are warranted to draw robust conclusions.

Introduction

Lung cancer is the most common cancer worldwide with ~1.8 million new patients diagnosed globally in 2012; and it is the leading cause of cancer-related mortality causing an estimated 1.6 million deaths in the same year [1,2]. Lung cancer is categorized into two broad classes: small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC). NSCLC accounts for about 85% of all malignancies originating from the lungs [3,4]. Despite advances in monitoring and diagnostic imaging techniques, nearly 40% of all NSCLC patients are diagnosed at advanced stages with distant metastasis [4,5].

In patients diagnosed with stage I, II or III NSCLC, treatment is generally with curative intent and usually includes a combination of surgery, radiation therapy (RT) and chemotherapy. However, in the case of stage IV patients in whom toxicity is a major concern, optimal management is not well-defined [6,7]. Currently, cytotoxic chemotherapy with a platinum-based doublet is the first-line treatment modality for patients with advanced NSCLC [7,8]. Although several regimens have demonstrated very similar efficacy in large phase III trials, at present, carboplatin combined with paclitaxel is a commonly administered combination regimen, due to more favorable toxicity profile of carboplatin allowing administration on an outpatient basis [9]. In addition, the use of immunotherapy for advanced NSCLC is newly immerging in the field and has been started to be integrated into the first line treatment [10–14].

Over the past decade, several trials have been conducted to evaluate different schedules of carboplatin/paclitaxel administration with the aim of enhancing efficacy and tolerability [7,15–18]; however, trials focusing on patients with impaired performance status and related comorbidities are lacking [19].

Unlike normally differentiated cells, cancer cells exhibit a dysregulated energy metabolism. Similar to normal developing cells and proliferating cells, they exhibit an increased glucose uptake leading to the lactate production, even in the presence of oxygen [20]. This phenomenon is called the
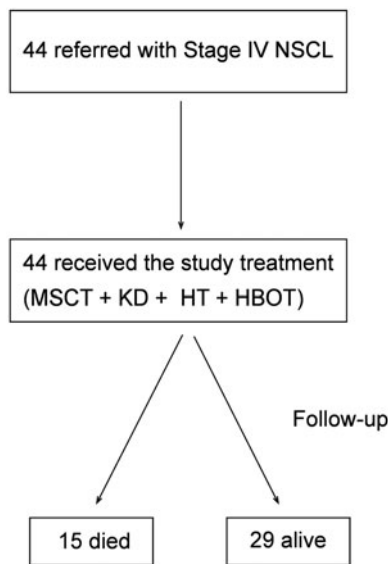
Figure 1. Study diagram. MSCT: metabolically supported chemotherapy; KD: ketogenic diet; HT: hyperthermia; HBOT: hyperbaric oxygen therapy. Patients were referred with stage IV disease to our clinic and all were eligible for our standard protocol upon admission.

'Warburg effect'. It was first recognized by Otto Warburg in 1924 who hypothesized that 'cancer is a disease of metabolic dysregulation' [21,22]. This abnormal energy metabolism is seen in almost all types of tumors [23] and is the basis of fluorodeoxyglucose-PET scan, one of the most important imaging techniques used in the diagnosis and follow-up of cancer. Several studies have focused on therapeutic strategies that will target this metabolic difference of cancer cells compared to normal cells; and ultimately this research has led to the development of metabolically supported chemotherapy (MSCT), a novel chemotherapy application method based on Warburg's hypothesis [24–26]. In practice, MSCT involves a 12-h fasting starting the previous evening and the administration of pharmaceutical doses of regular insulin prior to the administration of chemotherapy. This strategy aims to develop mild hypoglycemia in an attempt to cause an acute metabolic stress on cancer cells as well as to increase the efficacy of chemotherapeutic drugs by increasing membrane permeability [27]. The glucose dependency of cancer cells forms the rationale of adapting a diet that will decrease circulating glucose levels. The ketogenic diet, a high-fat, carbohydrate-restricted diet, decreases blood glucose levels, elevates blood ketone levels, and it has been shown to slow the progression of cancer [26,28–34].

Hyperthermia, locally increasing body temperature to 42 °C or higher, exploits heat sensitivity of cancer cells and causes direct cytotoxicity. Hyperthermia has been shown to increase the efficacy of radiotherapy and some chemotherapeutic agents by sensitizing cancer cells to these therapies; and some chemotherapeutic agents have shown synergism with hyperthermia, including both carboplatin and paclitaxel [25,26,35–43].

The abnormal vasculature of tumors causes tumor hypoxia, which increases the glycolytic dependence of cancer cells, has cancer-promoting effects and is also shown to promote resistance to chemotherapy and radiotherapy [44–48].

Administration of oxygen at elevated pressure during hyperbaric oxygen therapy (HBOT) results in better oxygenation of tumor cells; thus, counteracting unfavorable consequences of hypoxia. Several experimental studies provided supporting evidence for its potential use [33,34,49–53]; and a number of clinical studies demonstrated its benefit when used in combination with chemotherapy and radiotherapy for the treatment of various malignancies [35,36,54].

Based on the abovementioned supporting evidence, MSCT, ketogenic diet, hyperthermia and HBOT could work together by targeting several overlapping metabolic pathways and vulnerabilities of cancer cells. So far, no study has reported the impact of this novel combinatorial therapeutic strategy in managing stage IV NSCLC.

This study aimed to evaluate the efficacy and the tolerability of MSCT with carboplatin and paclitaxel combined with ketogenic diet, hyperthermia and HBOT in the treatment of stage IV NSCLC patients.

Materials and methods

Study design and patient selection

This retrospective single-center study included 44 patients diagnosed with stage IV metastatic NSCLC and received MSCT with carboplatin and paclitaxel between March 2010 and June 2015. Patients also received ketogenic diet, hyperthermia application and hyperbaric oxygen therapy concurrently with MSCT. Patients were identified through screening our patient database and a comprehensive evaluation of the medical records. Patients deemed eligible were those with biopsy-proven NSCLC, measurable disease as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) [55], and radiologically-proven stage IV disease. All patients had been referred to our clinic with stage IV NSCLC during the study period and all received the study treatment which is standard for our clinic (Figure 1). All patients with brain metastasis received radiotherapy. However, all of them had a measurable brain tumor at the time of starting study treatment.

Patients received a metabolically supported combination of carboplatin and paclitaxel in an outpatient setting on days 1 and 8 of every 3-week cycle (qw3) as first-line treatment. Eight cycles were planned for each patient. They were recommended to adopt a ketogenic diet continuously throughout cycles and follow-up period. They fasted overnight for 12 h, and blood glucose levels were measured upon admission in the morning. Then the blood sugar was decreased by insulin administration. HBOT and hyperthermia was given the same day or the next day sequentially after chemotherapy. Preferentially, hyperthermia was given first, but the two were never given at the same time [35,36]. Patient and survival data were extracted from the records and analyzed.

Metabolically supported chemotherapy

Premedication consisted of 45.5 mg pheniramine maleate, 0.25 mg palonosetron HCl and regular insulin (Humulin® R)
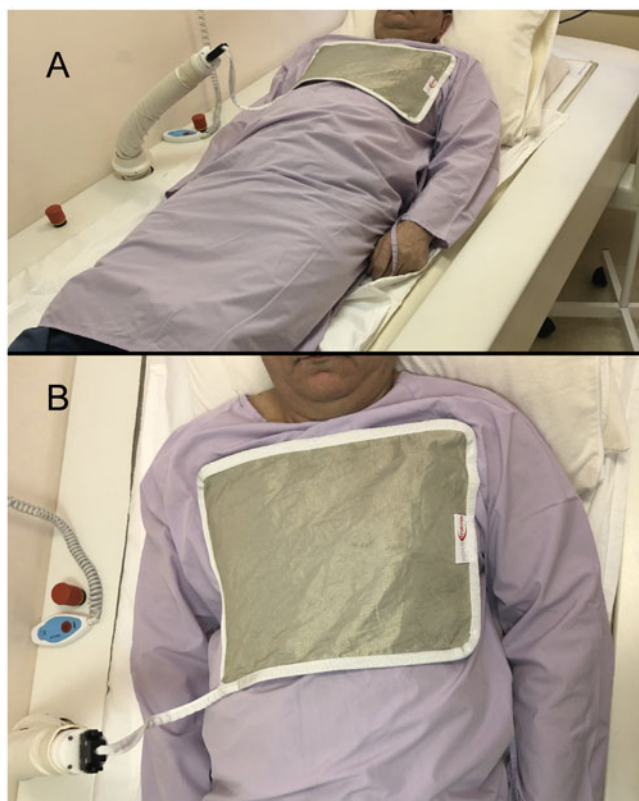
Figure 2. Placement of hyperthermia electrode. View from left (A) and above (B).

in doses ranging between 5 and 20 IU (in order to achieve a state of mild hypoglycemia with blood glucose levels around 50–60 mg/dl for normoglycemic patients and in accordance with MSCT protocols) [24–26].

Patients visited our clinic for treatment sessions following 12 h of fasting, and their blood glucose level was measured upon admission. Then this level was down-titrated to the targeted pretreatment mild hypoglycemia level with insulin administration. An IV line for dextrose administration was always kept open. Patients were closely monitored for hypoglycemia signs/symptoms and blood glucose levels by the attending physician and an experienced nurse. In normoglycemic patients, fasting blood glucose levels upon admission ranged between 70 and 90 mg/dl, while the achieved pretreatment glucose ranged between 50 and 59 mg/dl. For diabetics on the other hand, a more individualized approach was adopted. In diabetics (14 patients, none of which were on insulin and all were on oral anti-diabetic therapy) blood glucose level was lowered to around 90 mg/dl based on the individual patient's condition. All diabetic patients were managed together with endocrinology specialist support. Fasting blood glucose levels ranged between 95 and 160 mg/dl for diabetic patients. For these patients, the achieved pretreatment levels ranged between 65 and 95 mg/dl. Following the achievement of target blood sugar level, treatment was initiated together with oral sugar intake. All patients received a chemotherapy regimen consisting of paclitaxel 75 mg/m2 (over 60 min) and carboplatin AUC 2 (after paclitaxel, over 30 min).

A complete blood count (CBC) and serum urea and creatinine analysis were required from all patients on the day of treatment, and full dose chemotherapy was administered only when the neutrophil count was >2000/µL, platelet count was >100 000/µL and hemoglobin was >9.0 g/dL. Carboplatin dosage was calculated using the Calvert formula before each chemotherapy session, based on creatinine values using the Cockcroft-Gault formula. In case of neutropenia, anemia and/or thrombocytopenia, treatment was postponed for approximately a week and supportive treatments as well as granulocyte-colony stimulating factors (G-CSF) were administered for 3 consecutive days. CBCs and blood biochemistry analyses, including renal function tests, were repeated in each patient at least once weekly. Red blood cell (RBC) transfusions and platelet transfusions were given when values below the specified thresholds were detected. Carboplatin and paclitaxel doses were reduced by 20–25% only during the subsequent treatment. In case of severe myelosuppression, unacceptable toxicity, deterioration of performance status or multiple delays, schedule individualization was allowed and doses were reduced up to 30%. Primary prophylaxis with G-CSF was not given. Chemotherapy was mostly administered in an outpatient setting; however, patients were hospitalized in case of Grade 3 or febrile neutropenia or Grade 3–4 infection.

Patients that achieved complete response (CR), partial response (PR) or stable disease (SD) status continued to receive maintenance therapy with the same regimen until death. Those with progressive disease were assigned to second-line chemotherapy with a single agent such as erlotinib, gemcitabine, or docetaxel. Patients with ALK fusion received targeted therapy as second-line treatment following progression after chemotherapy.

Ketogenic diet, hyperthermia and hyperbaric oxygen therapy

Patients were encouraged to consume a ketogenic diet, which is high in fat and low in carbohydrate. However, it is a mild rather than a strict ketogenic diet, where patients avoid food with a high amount of carbohydrates. Every patient received a brief training regarding the diet restrictions and was given a food list. All patients were asked to keep a dietary record. In addition to proactively encouraging and questioning the patient for the ongoing ketogenic diet, blood sugar levels were measured as a part of routine procedures before insulin administration at each visit. Based on blood sugar levels and dietary records (if the patient was able to complete successfully), a feedback was given to the patient at each visit on how effective the diet was and what modifications or precautions are still required.

For each 60-min hyperthermia session, OncoTherm EHY-3010 HT device (OncoTherm, Troisdorf, Germany) was used to gradually increase the temperature of the tumoral region. Thoracic tumors and thoracic metastases were targeted. A large enough mobile electrode positioned over the tumoral region was used based upon each individual patient's condition to cover the primary tumor and thoracic metastases (if

Table 1. Demographic and clinical characteristics of the patients at baseline.

Characteristic	$n = 44$
Age, year, median (range)	65 (35–87)
Age >65 years	20 (44.5%)
Male gender	39 (88.6%)
Histology	
Adenocarcinoma	34 (77.3%)
Squamous cell carcinoma	8 (18.2%)
Undifferentiated	2 (4.5%)[a]
Metastatic sites	
0–1	0 (0 %)
2	4 (9.1%)
≥3	40 (90.9%)
Brain metastases	18 (40.9%)
Mutation status	
EGFR	
Mutation present	0 (0%)
No mutation detected	29 (65.9%)
Not evaluated	15 (34.1%)
ALK fusion	
Fusion	5 (11.4%)
No fusion detected	24 (54.5%)
Not evaluated	15 (34.1%)
Smoking status	
Nonsmoker	6 (13.6%)
Smoker	38 (86.4%)
Diabetes	14 (31.8%)
Presence of any comorbidity	32 (72.7%)[b]
Performance status	
ECOG 0-1	8 (18.2%)
ECOG 2	21 (47.7%)
ECOG 3	15 (34.1%)
Second malignancy	1 (2.3%)[c]

Notes: Unless otherwise stated, data presented as n (%). EGFR: epidermal growth factor receptor; ALK: anaplastic lymphoma kinase; ECOG: Eastern Cooperative Oncology Group. [a]One large cell carcinoma and one bronchoalveolar carcinoma; [b]diabetes, hypertension or chronic obstructive pulmonary disease; [c]this patient had been diagnosed with bladder carcinoma before NSCLC.

Table 2. Treatment response by patient characteristics.

	ORR n (%)	SD n (%)	PD n (%)	p value
All patients ($n = 44$)	27 (61.4 %)	7 (15.9 %)	10 (22.7 %)	
Age (years)				
≤65 ($n = 24$)	15 (62.5 %)	4 (16.7 %)	5 (20.8 %)	.95
>65 ($n = 20$)	12 (60.0 %)	3 (15.0 %)	5 (25.0 %)	
Histology				
AC ($n = 34$)	21 (61.8 %)	6 (17.6 %)	7 (20.6 %)	.29
SCC ($n = 8$)	6 (75.0 %)	0 (0 %)	2 (25.0 %)	
UC ($n = 2$)	0 (.0 %)	1 (50.0 %)	1 (50.0 %)	
Performance status				
ECOG 0–1 ($n = 8$)	5 (62.5 %)	2 (25.0 %)	1 (12.5 %)	.62
ECOG ≥2 ($n = 36$)	22 (61.1 %)	5 (13.9 %)	9 (25.0 %)	
Metastatic sites				
0–1 ($n = 0$)	0 (0 %)	0 (.0 %)	0 (.0 %)	.25
2 ($n = 4$)	4 (100.0 %)	0 (.0 %)	0 (.0 %)	
≥3 ($n = 40$)	23 (57.5 %)	7 (17.5 %)	10 (25.0 %)	
Brain Metastases				
Yes ($n = 18$)	8 (44.4 %)	3 (16.7 %)	7 (38.9 %)	.09
No ($n = 26$)	19 (73.1 %)	4 (15.4 %)	3 (11.5 %)	
Smoking status				
Yes ($n = 38$)	25 (65.8 %)	4 (10.5 %)	9 (23.7 %)	.05*
No ($n = 6$)	2 (33.3 %)	3 (50.0 %)	1 (16.7 %)	

Notes: ORR: Overall Response Rate (Complete Response (CR)+Partial Response (PR)); SD: Stable Disease; PD: Progressive Disease; AC: adenocarcinoma; SC: squamous cell carcinoma; UC: undifferentiated carcinoma (including large cell carcinoma and bronchoalveolar carcinoma); ECOG: Eastern Cooperative Oncology Group. *$p = .048$ before rounding to two decimals.

any). However, metastases outside the thoracic cavity were not targeted. In all patients, a 30×40 cm mobile electrode was used for hyperthermia session (Figure 2). The objective of hyperthermia was to obtain a tumoral tissue temperature over $43\,°C$ at the tumor site as it is reported to be cytotoxic at such temperatures. The OncoTherm EHY-3010 HT device used in our patient group uses modulated electrohyperthermia (mEHT) approach to specifically heat malignant cells to provide effective heat within the tumor tissue while preserving healthy surrounding tissues including the skin and makes an indirect temperature estimation based upon the energy applied. In all sessions, per instructions of the manufacturer, the power was set at 110 Watt and at the end of a 60-min session the total energy applied ranged between 380.000 and 450.000 Joules (average 400.000 Joules). Based on this amount of applied energy, the indirect temperature estimation of the device ranged between 43.9 and 45.2 $°C$.

For each 60-min HBOT session, Quamvis 320 hyperbaric oxygen chamber (OxyHealth, California, US) was used. It is a soft-walled chamber with a 32-inch diameter when inflated. The chamber was pressurized using a clean air compressor which filters air to 0.01 microns and a 10 L/min O_2 concentrator to produce an operating pressure of 1.5 atmospheres absolute (ATA).

Assessment of response

Assessment of treatment response was based on radiographic evaluations at the end of each 3-month period or following administration of four cycles, according to criteria defined by RECIST 1.1 [55]. Radiological response was always evaluated by PET-CT, and MRI was added in case of brain metastasis.

Assessment of toxicity

Toxicity was evaluated in accordance with Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03) [56]. Adverse events (AEs) experienced by each patient per cycle were recorded. The worst overall AE grade per event type throughout the study period was documented for each patient.

Statistical analysis

Data were analyzed using IBM SPSS Statistics version 20.0 software (SPSS Inc., Chicago, IL). Descriptive data are presented in number (percentage), median (range), mean (95% confidence interval), where appropriate. Categorical variables were compared using Pearson's chi-square test. Overall survival was defined as the time elapsed between the date of the first administration of the treatment and death from any cause. Progression-free survival was defined as the time elapsed between the date of the first administration of the treatment and death from any cause or progression. Patients without event at the last follow up were censored. Survival rates were estimated using Kaplan–Meier analysis and intergroup comparisons were performed using log-rank test. Two-sided p values <.05 were considered as an indication of statistical significance.

Table 3. Mean survival rates by patient characteristics.

	OS		PFS	
	Months (95% CI)	p value[a]	Months (95% CI)	p value[a]
All patients (n = 44)	42.9 (34.0–51.8)		41.0 (31.1–50.9)	
Age (years)				
≤65 (n = 24)	47.1 (35.7–58.5)	.19	46.8 (34.7–58.9)	.10
>65 (n = 20)	32.9 (25.9–39.9)		26.6 (19.6–33.7)	
Histology				
AC (n = 34)	45.1 (34.9–55.4)	.47	43.6 (31.8–55.3)	.61
SCC (n = 8)	32.6 (18.5–46.7)		32.4 (18.2–46.6)	
UC (n = 2)	37.3 (31.9–42.7)		35.8 (27.5–44.1)	
Performance status				
ECOG 0–1 (n = 8)	63.9 (52.9–74.9)	**.009**	63.4 (51.6–75.2)	**.009**
ECOG ≥2 (n = 36)	33.0 (27.2–38.7)		29.4 (22.6–36.1)	
Brain metastases				
Yes (n = 18)	34.6 (24.4–44.9)	.09	30.9 (19.1–42.8)	.07
No (n = 26)	42.6 (34.9–50.3)		40.6 (32.3–48.9)	
Smoking status				
Yes (n = 38)	36.8 (30.6–43.1)	.53	33.9 (26.6–41.2)	.36
No (n = 6)	49.8 (31.6–68.0)		49.7 (31.3–68.0)	

Notes: OS: Overall Survival; PFS: Progression- free survival; AC: adenocarcinoma; SC: squamous cell carcinoma; UC: undifferentiated carcinoma (including large cell carcinoma and bronchoalveolar carcinoma); ECOG: Eastern Cooperative Oncology Group. [a]Log-rank test.

Results

Table 1 shows the clinical and demographical characteristics of the patients at baseline. Majority had ECOG performance status ≥2 (81.8%). Most patients (90.9%) had metastasis at more than two sites and 40.9% had brain metastasis.

Chemotherapy dose and modifications

A median of 118 mg/m^2 of carboplatin and 75 mg/m^2 of paclitaxel were administered and the median relative dose intensity was almost 100% throughout 8 cycles for each patient. Twenty-one dose delays, 15 dose reductions and 12 schedule individualizations were required during 8 cycles.

Treatment response

Table 2 shows treatment response rates by patient characteristics after the completion of 8 cycles of therapy. In the whole study population, overall response rate (ORR, complete response plus partial response) was 61.4%; whereas, 15.9% and 22.7% of patients had SD and PD, respectively. Among the patient characteristics evaluated, only smoking status had a marginally significant relation with the distribution of treatment response (p = .048).

Survival estimates

At the end of 8 cycles of treatment, 42 out of 44 patients (95.4%) were alive and had completed 8 cycles of treatment. Two patients died after receiving 3 cycles of treatment. At the termination of follow-up (15 January 2016), 29 patients were alive (65.9%). Mean overall survival (OS) was 42.9 months (95% CI: 34.0–51.8). Corresponding figure for progression-free survival (PFS) was 41.0 months (95% CI: 31.1–50.9).

Table 3 shows mean survival rates (OS and PFS) by patient characteristics. A higher ECOG status (ECOG ≥2) was associated with worse OS (33.0 vs. 63.9 months, p = .009) and PFS (29.4 vs. 63.4 months, p = .009). On the other hand, age, histology, presence of brain metastasis and smoking had no effect on survival outcome. Figure 3 shows Kaplan–Meier curves for OS. In addition, a subgroup analysis of patients with available ALK fusion data (n = 29) showed numerically better overall survival (61.2 vs. 34.9 months) and progression-free survival rates (61.1 vs. 30.1 months) for patients with fusion (n = 5) than patients without fusion (n = 24); however, the difference did not reach statistical significance (p = .103 and .085, respectively).

Toxicity

During the treatment period, following hematological toxicities developed: grade 3 neutropenia, 3 (6.8%) patients; grade 3 anemia requiring RBC transfusions, 10 (22.7%) patients; grade 4 thrombocytopenia requiring platelet transfusion, 3 (6.8%) patients; and grade 5 neutropenia resulting in death, 1 (2.3%) patient.

Overall, non-hematological toxicities were rare. The most common non-hematological toxic events were grade 3 fatigue (n = 5, 11.3%) and diarrhea (n = 8, 18.2%). Only one patient (2.3%) developed grade 3 neuropathy. The most significant and lethal non-hematological toxicities, on the other hand, were grade 4 and 5 infections (specifically pneumonia and resulting pulmonary insufficiency), accounting for the deaths of 4 (26.7%) out of the 15 patients that died during the study period. During 8 cycles of treatment, no adverse effects or toxicities related to fasting, hypoglycemia, ketogenic diet, hyperthermia or hyperbaric oxygen therapy were observed.

Discussion

This retrospective study for the first time evaluated the efficacy and tolerability of weekly carboplatin/paclitaxel combination administered in a metabolically supported fashion together with ketogenic diet, hyperthermia and HBOT, in patients with metastatic NSCLC. Our findings support the benefits of integrating additional modalities targeting multiple tumor cell vulnerabilities into a chemotherapy schedule.

To date, several large studies have tested the efficacy and safety of carboplatin/paclitaxel regimen in advanced stage NSCLC (Table 4) [9,15,19,57–59]. Different administration schedules ranging from weekly regimens with more frequent sessions to 3-weekly regimens with less frequent and high per session dose were used. Among these studies, Volk et al. used a chemotherapy regimen similar to the present study [19]. In that study, patients with impaired ECOG performance (≥2) had worse survival, which is in line with our findings. However, reported response and survival rates were lower. Present study included patients with relatively unfavorable characteristics: majority had impaired performance status, all had distant metastasis, around 40% had brain metastasis. Despite this poor patient profile, the response and survival
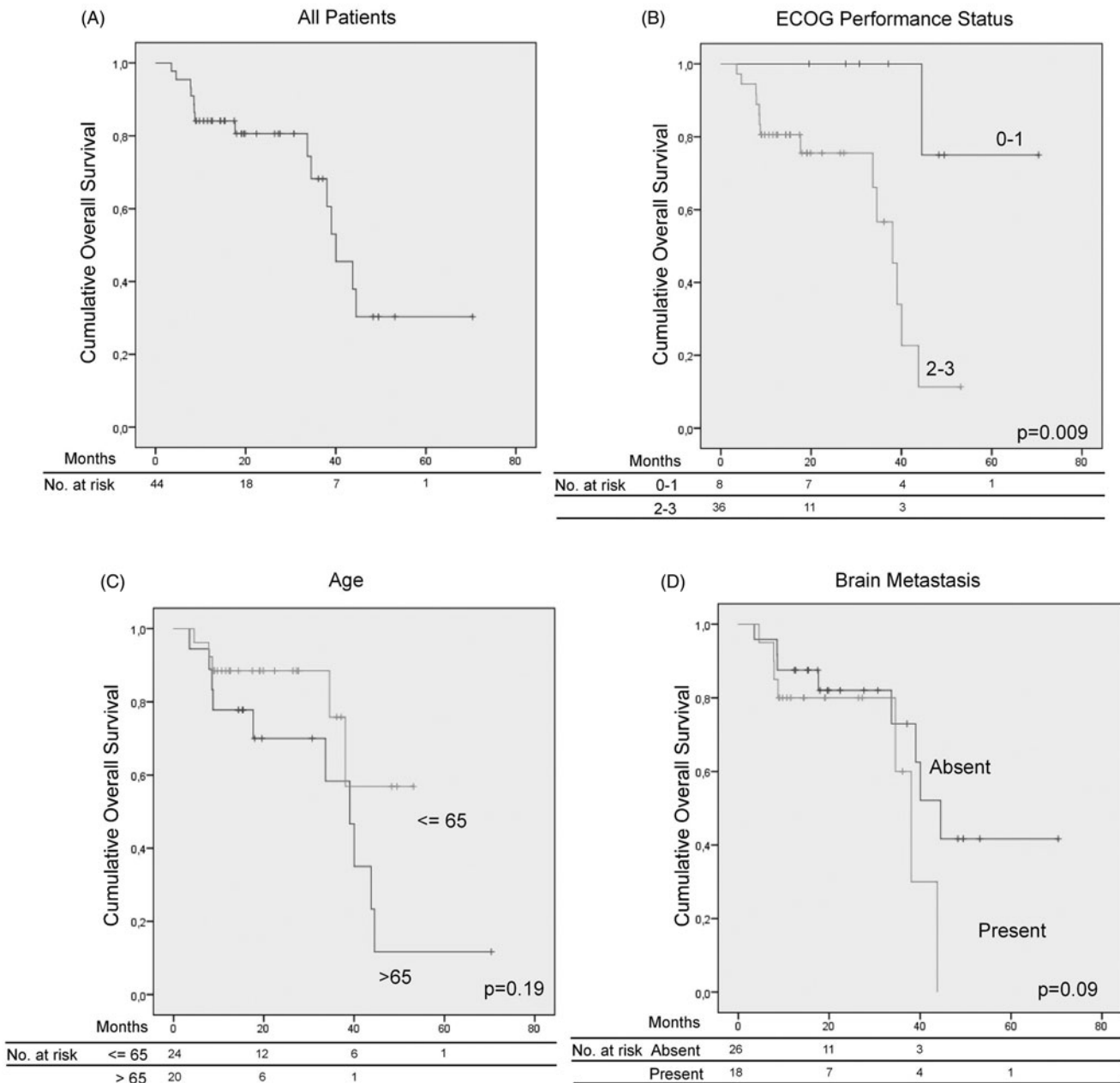
Figure 3. Kaplan–Meier curves for overall survival: (A) all patients; and patients stratified by ECOG performance status (B), age (C), and presence of brain metastasis (D). *p* values are calculated with Log-rank test. A higher ECOG status (ECOG ≥2) was associated with worse overall survival (Panel B, *p* = .009). However, older age (Panel C) and the presence of brain metastasis (Panel D) did not have an effect on overall survival outcome (*p* > .05 for both).

rates (ORR: 61.4%, OS: 42.9 months, PFS: 41.0 months) seem encouraging when compared to previous studies with carboplatin/paclitaxel combination as well as a recent study that evaluated the efficacy of atezolizumab, an anti-programmed death ligand-1 (PD-L1) antibody, in combination with platinum-based doublet [60]. Administration of paclitaxel more frequently but at a lower dose (potentially resulting in a continuous damage on tumor cell) as well as the addition of modalities with potential benefit (metabolically supported administration, ketogenic diet, hyperthermia and HBOT) to target multiple susceptibilities of cancer cell may all account for these encouraging results.

The treatment was also well tolerated. For example, no treatment discontinuation was required, in contrast to the 34% discontinuation reported by Volk et al. during the first

cycle [19]. Hematological and non-hematological toxicities were rare; and few dose delays, dose reductions or dose individualizations were required. No problems were encountered due to additional modalities.

Previous studies with MSCT regimens reported encouraging findings in patients with various types of malignancies. Standard gemcitabine-based and/or FOLFIRINOX protocol was successfully administered to patients with unresectable ductal pancreatic adenocarcinoma using a metabolically supported strategy with promising survival outcomes [24]. In an 81-year old patient with locally advanced rectal cancer, FOLFOX6 regimen administered using MSCT approach provided complete clinical and pathological response [25]. Similarly, complete clinical, radiological and pathological responses were achieved in a stage IV triple negative breast

Table 4. Comparison with other studies evaluating carboplatin /paclitaxel combinations in NSCLC patients.

Regimen	Current study Weekly regimens P 75 mg/m² days 1, 8, q3w C AUC 2 days 1, 8, q3w	Volk et al. [19] P 75 mg/m² days 1, 8, 15 q4w C AUC 3 days 1, 8, 15 q4w	Belani et al. [57] P 100 mg/m² days 1, 8, 15 q4w C AUC 6 day 1, q4w	Belani et al. [58] P 100 mg/m² days 1, 8, 15 q4w C AUC 6 day 1, q4w	Schuette et al. [59] P 100 mg/m² days 1, 8, 15, 22, 29, 36 q8w	Kelly et al. [9] 3-weekly regimens P 225 mg/m² day 1, q3w C AUC 2 days 1, 8, q3w	Schiller et al. [15] P 225 mg/m² day 1, q3w C AUC 6 days 1, q3w
n	44	190	132	223	457	206	290
Age (years)							
median	65	66	65	65	32	62	63
range	35–87	39–88	42–87	28–84	n.a.	26–80	30–85
≥70 years of age (%)	25	39	28[a]	n.a.	n.a.	n.a.	n.a.
Stage (%)							
III	0	7	23.5	18	26	12	14
IV	100	93	76.5	82	69	88	86
ECOG PS (%)							
0–1	18.2	81	85.6	84	91	100	95
≥2	81.8	19	14,4	12	6	0	5
Brain metastasis (%)	40.9	27	n.a.	n.a.	0	0	12
Efficacy							
ORR (%)	61.4	34,4	32	27,6	38	25	17
PFS (months)	41.0	3,4	6,9	4,6	6.1	4	3.1
OS (months)	42.9	6.3	11.3	9.7	8.9	8	8.1
Toxicity							
Neuropathy ≥ grade 3 (%)	2.3	6	5	12[b]	4	13	10
Neutropenia ≥ grade 3 (%)	6.8	14	22	13	17	57	63

Notes: P: paclitaxel; C: carboplatin; n.a.: no data available; ECOG PS: Eastern Cooperative Oncology Group performance status; ORR: overall response rate (complete response (CR)+partial response (PR)); PFS: progression-free survival; OS: overall survival. [a]Proportion of patients ≥70 years of age in the whole study population (111of 390 patients); [b]Only grade 2–3 neuropathy observed.

cancer patient treated with a MSCT regimen combining docetaxel, doxorubicin, cyclophosphamide as well as other treatment modalities [26].

In metabolically supported approach, several mechanisms seem to play a role in improving the efficacy of chemotherapy. Firstly, induced hypoglycemia may cause an acute metabolic stress on cancer cells, which have dysregulated metabolism and increased glucose dependency [21–23,61–63]; thus, making them vulnerable to treatment. Secondly, insulin may facilitate the action of chemotherapeutics at the cellular level through increasing membrane fluidity and permeability [64–66]. Adsorption of drug molecules onto insulin and the formation of drug-insulin complexes later internalized by receptor-mediated endocytosis may facilitate drug penetration, thereby enhancing the cytotoxic effects of chemotherapeutics [67–70]. Thirdly, cancer cells have an increased number of insulin and insulin-like growth factor (IGF) receptors on their cell membranes when compared to healthy cells: breast cancer cells, for example, have approximately seven times more insulin receptors [71] and ten times more IGF receptors [72]. The reaction between insulin and these receptors has the potential to extend the S-phase of the cell cycle, thereby rendering cancer cells more susceptible to the cytotoxic effects of chemotherapeutics for longer periods [73]. In addition, the lower concentration of insulin and IGF receptors on normal cells may relatively spare them from the cytotoxic effects of chemotherapeutics, possibly resulting in improved safety and tolerability.

In this study, besides MSCT, patients also adopted a ketogenic diet and received local hyperthermia and HBOT. These additional modalities might have contributed to the higher than expected survival and response outcomes. The strong dependence of cancer cells on glucose makes them vulnerable to a ketogenic diet that lowers blood glucose levels while elevating levels of circulating ketone bodies. Although the ketogenic diet has been used for decades as a treatment for intractable pediatric epilepsy, its potential as a therapy for targeting energy metabolism in cancer cells has only recently been explored. In the last decade, several pre-clinical studies and case reports provided support for its safety and role in slowing the progression of cancer, which have been encouraging for its use in cancer treatment [26,28–34,74–79]. Although findings of some studies suggest that ketone bodies may be used as fuel by cancer cells [80–82], a large body of evidence suggests the opposite. In these three papers, genetically altered culture systems were used; however, there is no evidence that this occurs naturally in cancer cells *in vitro* or in tumors *in vivo*. On the other hand, previous evidence strongly suggests that cancer cells cannot effectively use ketones for fuel [83–86], instead, they may have anti-tumoral effects [86–92].

Hyperthermia *per se* is cytotoxic at temperatures >43 °C and HBOT exploits the reliance of tumor cells on glycolysis, a major contributor to the upregulation of antioxidant activity responsible for the increased resistance of the tumor to prooxidant chemotherapy and radiation therapies [93]. The synergism between these therapies (ketogenic diet, hyperthermia, HBOT) [23,26,33–36] and their effectiveness in increasing the efficacy of conventional therapies have been reported in several studies [26,35–41,51–54]. In NSCLC patients, Ohguri et al. administered carboplatin/paclitaxel chemotherapy regimen together with hyperthermia and HBOT; and they

reported the protocol as being a feasible and promising modality for treating NSCLC patients [35]. A recent study evaluated the effect of concurrent administration of these three modalities with MSCT in a stage IV triple negative breast cancer patient with remarkably good response [26].

This study has several limitations. It is a retrospective study which is prone to bias particularly in terms of underreporting treatment variations (dose delays, dose reductions and schedule individualizations) as well as toxicities. This study has a small sample size, particularly when compared to previous studies with stage IV NSCLC patients. It is another limitation, probably not allowing sufficient power to detect some significant differences between risk subgroups. Therefore, the results should be interpreted cautiously, particularly when generalizing the results to advanced stage NSCLC patients. This study included all patients admitted with stage IV NSCLC and received the study treatment; thus, selection bias is unlikely. However, our institution is a small sized private institution serving primarily to high-income individuals with high education level, which might have favorably affected clinical outcomes due to probably improved patient compliance. Therefore, again, cautious generalization of our favorable survival outcomes to the general NSCLC stage IV patient population would be sensible. In addition, assessment of physiological and biochemical effects of ketogenic diet, hyperthermia and HBOT would not only give an idea of patient compliance particularly for the ketogenic diet, but also would shed light over potential unique mechanism and effect of each treatment component.

Main clinical implication of this study is that it emphasizes the importance of additional modalities in complementing chemotherapy in patients with advanced disease, provided that these complementary therapies are based on a rationale at a cellular or pharmacological level.

In conclusion, based on the encouraging outcomes of the patients included in the current study, MSCT with weekly carboplatin/paclitaxel together with a ketogenic diet, hyperthermia and HBOT appears to improve the outcomes of patients diagnosed with stage IV NSCLC. However, further research and comparative clinical trials are warranted to support and standardize this novel combinatorial treatment protocol as well as to identify the relative contribution of each component to the outcomes.

Disclosure statement

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