Long-Term Survival Outcomes of Metabolically Supported Chemotherapy with Gemcitabine-Based or FOLFIRINOX Regimen Combined with Ketogenic Diet, Hyperthermia, and Hyperbaric Oxygen Therapy in Metastatic Pancreatic Cancer

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Abstract

Background: Despite introduction of new chemotherapeutic agents, outcomes of patients with metastatic pancreatic cancer are still poor. Metabolically supported chemotherapy (MSCT) is a novel approach targeting dysregulated energy mechanism of the tumor cell. *Objectives:* This study aimed to examine the efficacy of metabolically supported administration of chemotherapy combined with ketogenic diet, hyperthermia, and hyperbaric oxygen therapy (HBOT) in patients with metastatic pancreatic cancer. *Method:* This retrospective observational study included 25 patients with metastatic pancreatic ductal carcinoma (stage IV) who received MSCT (either gemcitabine-based or FOLFIRINOX regimen administered concomitantly with induced hypoglycemia) plus ketogenic diet, hyperthermia, and HBOT combination. Survival outcomes were evaluated. *Results:* During the mean follow-up duration of 25.4 ± 19.3 months, median overall survival and median progression-free survival were 15.8 months (95% CI, 10.5–21.1) and 12.9 months (95% CI, 11.2–14.6), respectively. Age and gender did not have any effect on overall survival ($p > 0.05$ for all). *Conclusions:* MSCT administered together with ketogenic diet, hyperthermia, and HBOT appears to be a viable option with the potential to improve survival outcomes in patients diagnosed with metastatic pancreatic cancer. Further research, particularly with larger comparative clinical trials, is warranted.

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Langzeitüberlebens-Outcomes der metabolisch unterstützten Chemotherapie mit Gemcitabin oder FOLFIRINOX in Kombination mit ketogener Ernährung, Hyperthermie und hyperbarer Sauerstofftherapie beim metastasierenden Pankreaskarzinom

Schlüsselwörter

Metabolisch unterstützte Chemotherapie · Ketogene Ernährung · Hyperthermie · Hyperbare Sauerstofftherapie · Duktales Pankreaskarzinom · Metastasierung

Zusammenfassung

Hintergrund: Trotz der Einführung neuer Chemotherapeutika sind die Verlaufsaussichten von Patienten mit metastasierendem Pankreaskarzinom weiterhin ungünstig. Die metabolisch unterstützte Chemotherapie (metabolically supported chemotherapy, MSCT) ist ein neuartiger Ansatz, der auf den entgleisten Energiehaushalt der Tumorzelle abzielt. *Ziele:* Ziel dieser Studie war die Unter-

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suchung der Wirksamkeit einer MSCT in Kombination mit ketogener Ernährung, Hyperthermie und hyperbarer Sauerstofftherapie (HBOT) bei Patienten mit metastasierendem Pankreaskarzinom. ***Methoden:*** In dieser retrospektiven Beobachtungsstudie betrachteten wir 25 Patienten mit metastasierendem duktalem Pankreaskarzinom (Stadium IV), die mit einer Kombination aus MSCT (Gemcitabin-haltiges oder FOLFIRINOX-Schema, verabreicht unter induzierter Hypoglykämie) mit ketogener Ernährung, Hyperthermie und HBOT behandelt wurden. Verschiedene Überlebenskennzahlen wurden ausgewertet. ***Ergebnisse:*** Während eines mittleren Nachbeobachtungszeitraums von 25,4 ± 19,3 Monaten betrug das mediane Gesamtüberleben 15,8 Monate (95%-KI: 10,5–21,1) und das mediane progressionsfreie Überleben 12,9 Monate (95%-KI: 11,2–14,6). Alter und Geschlecht hatten keinen Einfluss auf das Gesamtüberleben ($p > 0,05$ für alle). ***Schlussfolgerungen:*** MSCT in Kombination mit ketogener Ernährung, Hyperthermie und HBOT scheint bei Patienten mit metastasierendem Pankreaskarzinom eine praktikable Behandlungsoption mit Potenzial zur Verbesserung von Überlebens-Outcomes zu sein. Weitere Forschung hierzu ist gerechtfertigt, insbesondere in Form größerer vergleichender klinischer Studien.

Introduction

Pancreatic cancer is an aggressive and deadly disease with a poor outlook. It ranks fourth and fifth among cancer-related deaths in the US and Europe, respectively [1, 2]. Long-term survival is usually not expected; e.g., in Europe, age- and area-adjusted 5-year relative survival rate is 6% [3]. Owing to its rapid course, unavailability of early detection tests, and absence of recognizable symptoms and signs in early disease, many patients are diagnosed late in the disease course, either with metastatic or locally advanced disease [2].

Chemotherapy confers survival advantage over best supportive care in cases with advanced disease [4]. In patients with locally advanced and metastatic pancreatic cancer, gemcitabine monotherapy or gemcitabine-based combination therapies are recommended by recent guidelines [5]. Two recent meta-analyses demonstrated superior survival outcomes with gemcitabine-based combination therapies when compared to gemcitabine alone but with increased toxicity [6, 7]. FOLFIRINOX regimen is also considered an option for these patients [8].

In 1924, Otto Warburg hypothesized that "cancer is a disease of metabolic dysregulation." Since then, this dysregulated energy metabolism evident in almost all tumor types where aerobic fermentation compensates for insufficient oxidative phosphorylation has been named the "Warburg effect" [9–11]. Metabolic impairment characterized by glucose dependency and increased lactate production in cancer cells has been linked to mitochondrial dysfunction and genetic mutations [11–14]. This feature also forms the basis of fluorodeoxyglucose-PET scans used in the diagnosis and follow-up of cancer.

Based on this metabolic difference between cancer cells and normal cells, a novel chemotherapy administration method, namely metabolically supported chemotherapy (MSCT), has been developed [15–17], which involves a 12-hour fasting before each chemotherapy session and administration of insulin just prior to chemotherapy in an attempt to increase the efficacy of chemotherapeutic drugs by increasing membrane permeability [18] and for the development of mild hypoglycemia to cause an acute metabolic stress on cancer cells. Ketogenic diet is a supplementary approach also targeting metabolic vulnerability of cancer cells through decreasing the availability of glucose. Adapting a ketogenic diet has been shown to slow the progression of cancer [17, 19–25].

Another supplementary approach, hyperthermia, has been shown to increase the efficacy of radiotherapy and chemotherapy by sensitizing cancer cells to these therapies, and synergism between hyperthermia and many chemotherapeutic agents have already been demonstrated [15, 17, 26–34].

Tumor hypoxia due to abnormal vasculature has cancer-promoting effects and has been associated with resistance to chemotherapy and radiotherapy [35–39]. During hyperbaric oxygen therapy (HBOT), oxygen is administered at high pressure resulting in better oxygenation of tissues. Better oxygenation has the potential to counteract such unfavorable consequences of hypoxia in tumor cells, thus improving the efficacy of chemotherapy. Evidence supporting its potential use comes from a number of experimental [24, 25, 40–44] and clinical studies [26, 27, 45].

Available evidence supports the potential benefits of MSCT, ketogenic diet, hyperthermia, and HBOT. A combination of the four could work synergistically by targeting several overlapping metabolic pathways and vulnerabilities of cancer cells.

This study aimed to examine the efficacy of MSCT combined with ketogenic diet, hyperthermia, and HBOT in patients with metastatic ductal pancreatic cancer and hypothesized that this combination therapy is associated with favorable survival and clinical outcomes.

Materials and Methods

Study Design and Patient Selection
This retrospective observational single-center study included 25 patients diagnosed with stage IV pancreatic cancer who received MSCT with a gemcitabine-based regimen or FOLFIRI-

Fig. 1. Schematic representation of each chemotherapy session showing treatment order. Patients are admitted after 12 h of fasting. Upon admission, insulin is administered to obtain mild hypoglycemia, after which chemotherapy is administered. Hyperthermia and HBOT are administered within 24 h of chemotherapy application or both are administered on the next day. On a gemcitabine-based chemotherapy regimen, chemotherapy is administered on day 1 and day 8 of a 21-day cycle, and on a FOLFIRINOX chemotherapy regimen, chemotherapy is administered on day 1 every 2 weeks. Ketogenic diet is adapted by the patients throughout the whole treatment period.
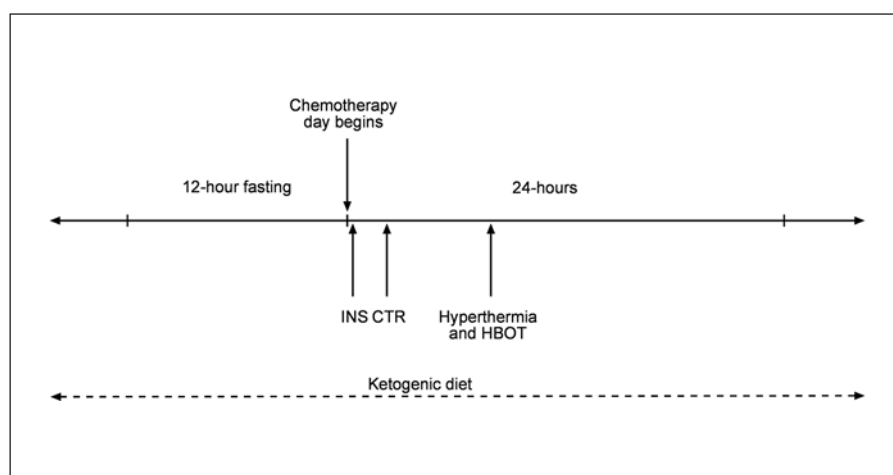
NOX between July 2012 and August 2014. In addition, patients adapted a ketogenic diet and received hyperthermia application and HBOT together with MSCT. Patients with metastatic pancreatic cancer at the time of admission were included in the study. Regardless of previous disease or treatment course, presentation with metastatic disease was considered the time of diagnosis. A prospectively maintained institutional database for MSCT was screened to identify eligible patients. Patients with biopsy-proven pancreatic cancer, measurable disease as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) [46], and radiologically proven stage IV disease were included for analyses. Patients eligible for chemotherapy were also considered eligible for other modalities (metabolic administration, ketogenic diet, HBOT, and hyperthermia) when making treatment planning. Patient and survival data were extracted from the records and analyzed. Primary endpoint was overall survival, whereas secondary endpoints were progression-free survival, response rates, and toxicity.

MSCT Protocol

Patients received either a standard gemcitabine-based regimen or the FOLFIRINOX regimen. Patients who previously progressed while receiving gemcitabine regimen preferentially received FOLFIRINOX regimen. Gemcitabine-based regimen included 1,000 mg/m^2 gemcitabine, 30 mg/m^2 cisplatin, and 400 mg/m^2 fluorouracil, which was administered on days 1 and 8 of a 21-day cycle. FOLFIRINOX regimen included 85 mg/m^2 oxaliplatin, 400 mg/m^2 folinic acid, 180 mg/m^2 irinotecan, and fluorouracil (400 mg/m^2 bolus then 2,400 mg/m^2 over 46 h), administered all on day 1 and then repeated every 2 weeks. Patients received these chemotherapy regimens until death as far as they tolerated. In case of disease progression as assessed by PET/CT imaging, patients receiving gemcitabine-based regimen were switched to FOLFIRINOX chemotherapy.

Patients were encouraged to consume a ketogenic diet throughout the treatment period. Before each chemotherapy session, patients fasted for 12 h. In addition, they received regular insulin (Humulin® R) as well as 45.5 mg pheniramine maleate and 0.25 mg palonosetron HCl, as premedication just prior to each chemotherapy administration. Insulin doses ranged between 5–20 IU with the aim to achieve a state of mild hypoglycemia for normoglycemic (nondiabetic) patients (50–60 mg/dL blood glucose levels) [15–17]. Hypoglycemia target was higher in patients with diabetes, corresponding to mild hypoglycemia based on the glycemic status of the patient. All patients were closely monitored for hypo-

glycemia signs/symptoms and blood glucose levels by experienced staff and an i.v. line for dextrose administration was always kept open. Chemotherapy administration was initiated together with oral sugar intake following the achievement of target blood sugar level.

Following each MSCT administration, patients received one session of hyperthermia and HBOT. Each hyperthermia session lasted for 60 min. OncoTherm EHY-3010 HT device (OncoTherm, Troisdorf, Germany) was used to increase the temperature of the tumoral region gradually. This device uses a modulated electrohyperthermia approach to specifically heat malignant cells and provides effective heat within the tumor tissue while preserving healthy surrounding tissues including the skin. Indirect temperature estimations are made based on the energy applied. The objective of hyperthermia was to obtain a tumoral tissue temperature over 43 °C at the tumor site. A large enough mobile electrode positioned over the tumoral region was used based on each individual patient's condition to cover the primary tumor and metastases. In case the disease was limited to the abdomen, a 30 × 40 cm mobile electrode was used. When the disease was also extended to the thorax, a larger 40 × 50 cm mobile electrode was used to cover the tumoral area. Metastases outside the abdomen and thoracic cavity were not targeted. Per instructions of the manufacturer, the power was set at 110 W for the 30 × 40 cm mobile electrode and at 130 W for the 40 × 50 cm mobile electrode. At the end of a 60-min session, the total energy applied was on average 400,000 Joules for the 30 × 40 cm mobile electrode and 460,000 Joules for the 40 × 50 cm mobile electrode.

Quamvis 320 hyperbaric oxygen chamber (OxyHealth, California, US) was used for each 60-min HBOT session, during which the patient was subjected to 1.5 atmospheres of pressure. Figure 1 shows a schematic representation of treatment order during each chemotherapy session.

Assessment of Toxicity

Evaluation of toxicity was done using Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03) [47]. Adverse events experienced by each patient per cycle were recorded and for each patient, the worst overall adverse event grade per event type throughout the study period was documented.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 21.0 software (SPSS Inc., Chicago, IL, USA). Overall survival was defined as the time elapsed between the date of diagnosis of metastatic dis-

Table 1. Demographical and clinical characteristics of the patients

Characteristic	$N = 25$
Median age (range), years	61 (41–81)
Male gender	17 (68.0)
Chemotherapy	
Only gemcitabine-based	7 (28.0)
Only FOLFIRINOX	10 (40.0)
Switch to FOLFIRINOX*	8 (32.0)

Unless otherwise stated, data is presented as *n* (%). * Patients receiving gemcitabine-based regimen were switched to FOLFIRINOX chemotherapy in case of disease progression.

ease and death from any cause. Patients alive at the last follow-up were censored. Progression-free survival was defined as the time elapsed between the date of diagnosis of metastatic disease and disease progression or death from any cause. Patients alive and free from progression at the last follow-up were censored. Survival rates were estimated using Kaplan-Meier analysis, and univariate comparisons were performed using log-rank test. Two-sided *p* values <0.05 were considered an indication of statistical significance.

Results

Table 1 shows demographical and clinical characteristics of the patients. Median age was 61 years (range, 41–81). More than two-thirds of the patients were male (68.0%). Tumor response rates at 3 months were as follows: complete response, 8 patients (32%); partial response, 15 patients (60%); stable disease, 1 patient (4%); progressive disease, 1 patient (4%).

Mean duration of follow-up was 25.4 ± 19.3 months (median 15.8, range 7.2–69.7 months). Median overall survival and median progression-free survival were 15.8 months (95% CI, 10.5–21.1) and 12.9 months (95% CI, 11.2–14.6), respectively. Figure 2 shows Kaplan-Meier curves for all patients.

Table 2 shows overall and progression-free survival rates by patient characteristics. Patients who initially received gemcitabine regimen had better survival outcomes compared to the patients who initially received FOLFIRINOX. Age and gender did not have any effect on survival outcomes.

During the study period, the following hematological toxicities developed: grade 3/4 neutropenia, 9 (36%) patients; febrile neutropenia, 1 (4%) patient; grade 4 thrombocytopenia requiring platelet transfusion, 4 (16%) patients; grade 3 anemia requiring RBC transfusions, 7 (28%) patients. Overall, non-hematological toxicities were rare. Two (8%) patients had grade 3 diarrhea. During the study period, no adverse effects or toxicities related to fasting, hypoglycemia, ketogenic diet, hyperthermia, or HBOT were observed.

Discussion

In this study, administration of MSCT together with ketogenic diet, hyperthermia, and HBOT resulted in encouraging survival outcomes in patients with metastatic pancreatic cancer. To date, only few studies have examined this combination in several malignant conditions. The findings of this study have clinical implications in terms of both patient care and future research on treatment modalities complementary to conventional chemotherapy.

In an earlier report, chemotherapy was associated with a significantly better but limited survival when compared to best supported care (median survival rate, 6 vs. 2.5 months) [4]. Later, better rates have been reported with different chemotherapy regimens, but results are far from being satisfactory. A meta-analysis comparing gemcitabine-based combinations and gemcitabine alone included 26 studies and 8,808 patients with unresectable pancreatic cancer and demonstrated a survival advantage for combination therapy. In that study, median overall survival ranged between 5.5 and 9 months in the gemcitabine-based combination therapy group [7]. In a large randomized trial comparing FOLFIRINOX and gemcitabine in patients with metastatic pancreas cancer, the median overall survival was 11.1 months and 6.8 months in the FOLFIRINOX group and gemcitabine group, respectively [8]. A recent review summarizes the findings of the randomized controlled trials that compared various combination therapies with gemcitabine monotherapy in patients with advanced metastatic cancer (not only metastatic cancer, as it is the case in the present study) and reported median survival rates ranging between 5.1 and 11.1 months and response rates ranging between 7 and 31.6% [48]. In this study, we administered similar chemotherapeutic agents but used a metabolically supported approach in combination with ketogenic diet, hyperthermia, and HBOT and achieved an encouraging overall median survival rate of 15.8 months and progression-free survival rate of 12.9 months. In addition, response rates at 3 months were also encouraging.

Although patients who received gemcitabine regimen first at the beginning of this study had better outcomes, this does not seem to represent a true difference between two chemotherapy regimens since patients who previously progressed while receiving gemcitabine regimen preferentially received FOLFIRINOX regimen as the initial therapy, thus representing a group of patients with different clinical course. Large prospective randomized studies are warranted to test any true difference between the two regimens.

MSCT is an approach aiming to supplement the chemotherapy regimen in terms of efficacy and safety. Induction of hypoglycemia to target increased glucose de-
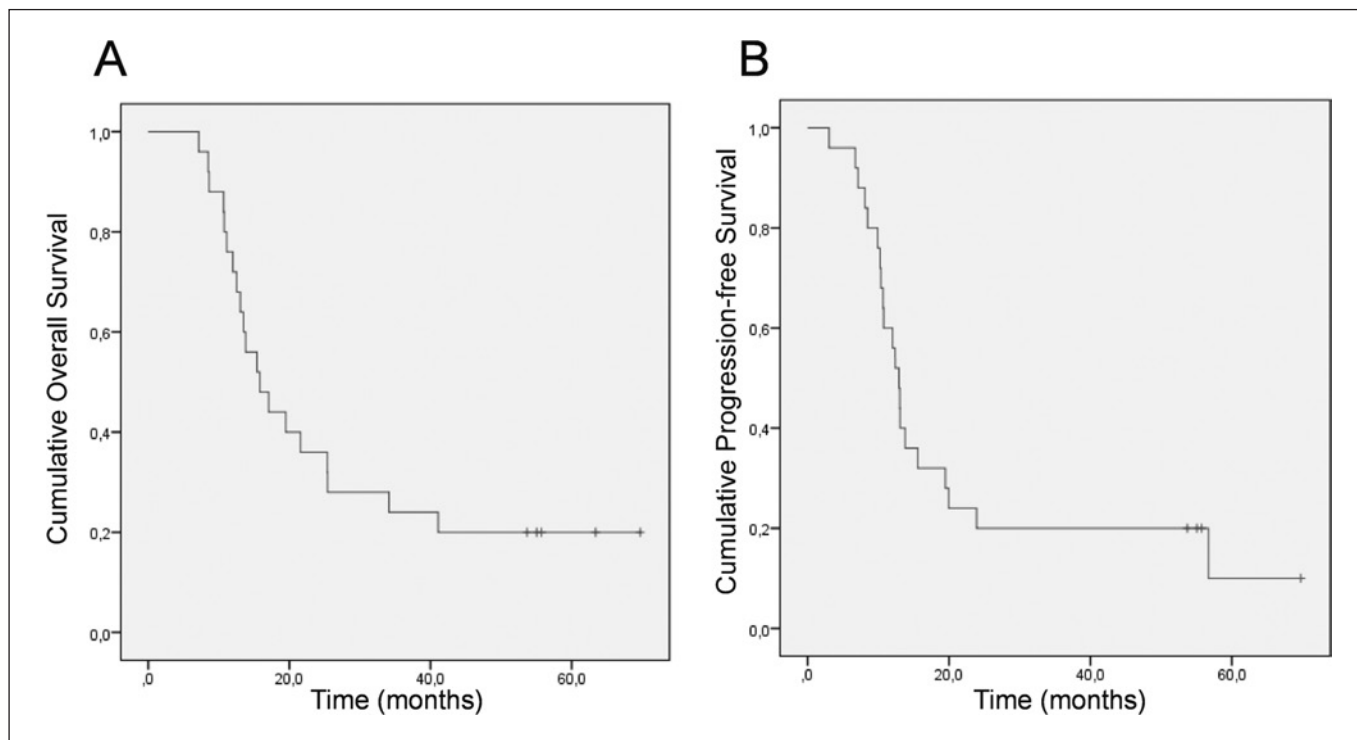
Fig. 2. Kaplan Meier curves for overall survival (**A**) and progression-free survival (**B**).

Table 2. Survival rates by patient characteristics

Characteristic	Mean (95% CI), months	Median (95% CI), months	p value[a]
Overall survival			
All patients (*n* = 25)	27.4 (18.6–36.3)	15.8 (10.5–21.1)	
Age			
≤ median (*n* = 13)	23.6 (13.4–33.9)	15.4 (11.6–19.3)	0.521
> median (*n* = 12)	30.4 (17.1–43.9)	19.5 (6.3–32.7)	
Gender			
Male (*n* = 17)	29.7 (18.4–41.0)	15.8 (10.4–21.2)	0.540
Female (*n* = 8)	20.6 (11.1–30.1)	13.8 (5.5–22.1)	
Initial chemotherapy regime*			
Gemcitabine-based (*n* = 15)	34.7 (21.9–47.4)	21.6 (11.1–32.1)	0.016
FOLFIRINOX (*n* = 10)	16.6 (9.5–23.7)	12.0 (9.2–14.8)	
Progression-free survival			
All patients (*n* = 25)	22.3 (13.9–30.7)	12.9 (11.2–14.6)	
Age			
≤ median (*n* = 13)	18.1 (8.4–27.8)	12.0 (8.4–15.6)	0.217
> median (*n* = 12)	27.4 (13.5–41.4)	13.8 (8.4–19.2)	
Gender			
Male (*n* = 17)	24.0 (13.2–34.7)	12.9 (9.8–16.0)	0.744
Female (*n* = 8)	17.6 (7.5–27.7)	12.4 (7.5–17.3)	
Initial chemotherapy regime*			
Gemcitabine-based (*n* = 15)	29.6 (17.1–42.1)	13.8 (5.5–22.1)	0.023
FOLFIRINOX (*n* = 10)	11.3 (7.8–14.8)	10.7 (10.1–11.2)	

[a] Log-rank test. * Regardless of which treatment(s) the patient received before the diagnosis of metastatic disease, the first treatment that the patient received at the beginning of this study.

pendency of the tumor cell is the main objective of MSCT, which in turn causes acute metabolic stress in tumor cells due to the low availability of circulating glucose [9–14]. In addition, the insulin molecule itself may have a direct contribution to the efficacy and safety of the MSCT. Insulin increases membrane fluidity and permeability; therefore, it has the potential to improve the transport of chemotherapeutics into the tumor cell and increase their cytotoxic effects [49–51]. Insulin-drug complexes internalized by receptor-mediated endocytosis seems to be important in this facilitated transport [52–55]. Insulin-receptor interaction would also prolong the S-phase of the cell cycle, therefore rendering cancer cells more susceptible to the cytotoxic effects of chemotherapeutics [56]. It is of note to emphasize that the effect of insulin at the cellular level, either in terms of facilitated transport of chemotherapeutics or prolonged S-phase, would be more pronounced in tumor cells compared to healthy cells owing to the increased amount of insulin and insulin-like growth factor (IGF) receptors on their membranes [57, 58]. This difference in receptor density would improve treatment specificity through augmented cytotoxic effects in tumor cells in contrast to relative protection of normal cells. So far, several studies have provided supporting evidence for the benefits of integrating metabolic support to chemotherapy regimens in patients with advanced cancer. The preliminary findings of this study were reported elsewhere previously with promising outcomes [16]. In addition, complete clinical and pathological response was achieved in an 81-year-old patient with locally advanced rectal cancer using FOLFOX6 regimen with MSCT approach [15]. In a stage IV triple-negative breast cancer patient treated with an MSCT regimen combining docetaxel, doxorubicin, and cyclophosphamide, complete clinical, radiological, and pathological response was also achieved [17].

Ketogenic diet, another additional modality used in this study, also targets glucose dependency of the tumor cell. Several preclinical studies and case reports have provided support for its potential role in the treatment of cancer [17, 19–25, 59–64]. Hyperthermia is itself cytotoxic and potentially sensitizes the tumor cell to chemotherapeutics. HBOT exploits the reliance of tumor cells on glycolysis, which contributes to the antioxidant activity responsible for the resistance of the tumor to pro-oxidant chemotherapy and radiation therapies [65]. Various combinations of these therapies have been shown to act synergistically and potentially complement the conventional therapies in different cancers [11, 17, 24–32, 42–45]. Ohguri et. al. [26] added hyperthermia and HBOT to the chemotherapy regimen in NSCLC patients with multiple pulmonary metastases and obtained promising results.

To the best of our knowledge, to date several studies have tested combinations of chemotherapy and hyperthermia (one of the components of our treatment protocol) in the treatment of pancreatic cancer. In a recent study from China, patients with pancreatic cancer received deep regional hyperthermia in addition to modified FOLFIRINOX regimen and hyperthermia treatment was performed during chemotherapy for 45 min in each session [66]. In that study, 82% of the cases had metastatic disease. Patient group and mode of hyperthermia administration is similar to our study. An overall survival rate of 17 months was reported, which is also similar to our findings. On the other hand, progression-free survival was relatively lower (4 months). In another study with locally advanced or metastatic pancreatic cancer patients with malignant ascites, mean overall survival of 6.5 months has been reported with the combination of chemotherapy (systemic and intraperitoneal) and abdominal hyperthermia [67]. Several earlier studies also reported encouraging results with the combination of chemotherapy and hyperthermia in the treatment of pancreatic cancer [68–71]. In addition, a recent study examined the same combinational treatment protocol used in this study (MSCT, ketogenic diet, hyperthermia, and HBOT) in patients with stage IV non-small cell lung cancer with a mean overall survival rate of 42.9 months, supporting the notion that targeting multiple pathways and cellular vulnerabilities may bring about remarkable improvements in the outcomes of patients with advanced cancer [72].

Regarding the timings of HBOT and hyperthermia, they are similar across several previous studies testing them in combination with chemotherapy. In the study by He et al. [66] for example, hyperthermia treatment was performed during chemotherapy for 45 min. Ohguri et al. [26] used HBOT and hyperthermia at each chemotherapy session. Iyikesici et al. [72] administered HBOT and hyperthermia just after chemotherapy. The rationale is to target multiple vulnerabilities of the tumor cell simultaneously and provide the highest possible stress on malignant cells.

The low sample size of this study might have prevented achieving sufficient power to detect survival differences between subgroups, which may be regarded as a major limitation. In addition, retrospective design is still another limitation, although all patients evaluated were treated uniformly and underwent systemic follow-up based on standard, predefined guidelines. Another limitation of the study is the lack of any quality of life measurements, which is planned to be incorporated into our future studies with this combinational treatment modality. However, observed safety and feasibility of the additional modalities does not seem to unfavorably effect the quality of life in this group of patients.

It is of note to emphasize that this study is preliminary in nature. Since we have some evidence on potential benefit of each component, we combine them in an attempt to provide best possible care for patients receiving treatment in our institution and this is the overall evaluation of the outcomes. Each component has some rationale based on previous studies, but relative contribution of each component may be subject to future larger prospective studies.

Advanced cancer is mostly associated with poor prognosis and available treatment modalities are limited. This study emphasizes that complementary therapies added to the conventional chemotherapy may be a viable option, particularly if they have a biochemical or pharmacological rationale.

Conclusion

Findings of this study suggest that MSCT administered together with ketogenic diet, hyperthermia, and HBOT is a viable option with the potential to improve survival outcomes of patients diagnosed with metastatic ductal pancreatic cancer. Further research and comparative clinical trials are warranted.

Statement of Ethics

Due to the retrospective nature of the study, institutional review board approval was not required. The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

The author of the manuscript made substantial contributions to the conception/design of the work and the acquisition, analysis, and interpretation of data, drafted the work and revised it critically for important intellectual content, approved the final version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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