Original Article

Survival Outcomes of Metabolically Supported Chemotherapy Combined with Ketogenic Diet, Hyperthermia, and Hyperbaric Oxygen Therapy in Advanced Gastric Cancer

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ABSTRACT

Background: Survival outcomes are still far from being satisfactory in patients with advanced gastric cancer, despite availability of novel chemotherapeutic regimens. **Aim:** This study evaluated the outcomes of patients with advanced gastric cancer who received chemotherapy along with additional treatment modalities targeting multiple tumor cell vulnerabilities. **Materials and Methods:** A total of 24 patients diagnosed with stage III–IV locally advanced or metastatic gastric adenocarcinoma that received metabolically supported chemotherapy (MSCT) combined with ketogenic diet, local hyperthermia, and hyperbaric oxygen therapy (HBOT) between April 2014 and October 2017 were included in this retrospective study. Survival outcomes were evaluated. **Results:** In 22 patients (88.0%), complete response was achieved. Mean duration of follow-up was 23.9 ± 12.7 months. Mean overall survival was 39.5 months (95% confidence interval [CI]: 28.1–51.0) and mean progression free survival was 36.5 months (95% CI: 25.7–47.2). No problems were encountered due to fasting, hypoglycemia, ketogenic diet, hyperthermia or HBOT. **Conclusions:** The combination treatment used in this study (MSCT together with a ketogenic diet, hyperthermia and HBOT) appears to be promising in the treatment of advanced gastric cancer. Further research and comparative clinical trials are warranted to support and standardize this novel treatment protocol.

Keywords: *Advanced gastric cancer, hyperbaric oxygen therapy, hyperthermia, ketogenic diet, metabolically supported chemotherapy*

Introduction

Gastric cancer represents a global health problem with substantial mortality and morbidity burden. In 2012, almost one million new cases were diagnosed with gastric cancer and >700,000 died.[1]

Surgery provides high cure rate for early stage disease (stage IA/B), but these patients represent a minority of the cases. Almost 80%–90% of patients are either diagnosed at an inoperable stage or develop recurrence after curative surgery; and patients with advanced disease with inoperable, recurrent or metastatic tumors have poor prognosis, even poorer without chemotherapy.[2] Currently, chemotherapy is the mainstay of treatment in advanced gastric cancer, although there is no consensus on the ideal regimen.[2]

The recent ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up of gastric cancer recommends doublet or triplet platinum/fluoropyrimidine combinations for fit patients with advanced/metastatic disease as first line treatment.[3] In addition, encouraging results have been obtained with regimens consisting of oxaliplatin, leucovorin, and 5-FU in patients with advanced gastric cancer.[4-12] However, the survival outcomes are still far from being satisfactory in this group of patients with poor outlook.

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In cancer cells, aerobic fermentation compensates for insufficient oxidative phosphorylation, a phenomenon first described by Otto Warburg who hypothesized that "cancer is a disease of metabolic dysregulation."[13,14] This abnormal energy metabolism characterized by glucose dependency and increased lactate production has been linked to mitochondrial dysfunction and genetic mutations.[15,16] Metabolically supported chemotherapy (MSCT) is a novel chemotherapy administration strategy targeting this metabolic difference of cancer cells.[17-19] In an attempt to increase membrane permeability for chemotherapeutic agents[20] and to develop mild hypoglycemia resulting in an acute metabolic stress on cancer cells, MSCT integrates 12-h fasting before each chemotherapy session and concomitant administration of insulin to the usual chemotherapy schedule. An additional approach to target glucose dependency of cancer cells is the adaption of a ketogenic diet, which has been shown to slow the progression of cancer.[19,21-25]

Hyperthermia causes direct cytotoxicity and has the potential to sensitize cancer cells to radiotherapy and chemotherapy as evidenced by previous studies.[17,19,26-30] Hyperbaric oxygen therapy (HBOT) involves the administration of oxygen at an elevated pressure resulting in better oxygenation of tissues. It has the potential to counteract unfavorable effects of hypoxia during chemotherapy and radiotherapy.[31-34] Several clinical studies demonstrated its benefit when used in combination with chemotherapy and radiotherapy for the treatment of various malignancies.[26,27,35]

MSCT, ketogenic diet, hyperthermia, and HBOT seem to have a synergistic action since they target overlapping metabolic pathways and vulnerabilities of cancer cells. Combination of these four modalities may prove more efficient when compared to chemotherapy alone. To date, no study has examined the role of this novel combinatorial therapeutic strategy in the management of gastric cancer.

This study aimed to evaluate the survival outcomes of patients with advanced gastric cancer who received MSCT with triplet taxane/platinum/fluoropyrimidine combination together with ketogenic diet, hyperthermia, and HBOT.

Materials and Methods

Study design and patient selection

This retrospective single-center study included 24 patients diagnosed with stage III–IV locally advanced or metastatic gastric adenocarcinoma that received MSCT combined with ketogenic diet, local hyperthermia and hyperbaric oxygen therapy between April 2014 and October 2017. The above-mentioned combination treatment used in this study is the routine treatment approach adopted in our clinic. Eligible patients were identified from the institutional database through screening of medical records of all patients diagnosed with gastric cancer (any class, stage, or subtype) and treated at our clinic during the study period; and the data were extracted retrospectively. Inclusion criteria were as follows: Biopsy-proven gastric cancer, measurable disease as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1),[36] radiologically proven stage III-IV disease, and receiving study treatment during the study period.

Study treatments

All patients were advised to adapt a ketogenic diet throughout the treatment period. Before each metabolically supported chemotherapy session patients fasted overnight and immediately before chemotherapy administration they received regular insulin (Humulin®R) 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 previous MSCT protocols).[17-19] All patients were administered a chemotherapy regimen consisting of docetaxel 25 mg/m^2 (over 60 min), carboplatin AUC 2 (over 30 min and subsequent to docetaxel), and 5-FU 600 mg/m^2. This combination treatment was administered in an outpatient setting and repeated on the first and eighth day of every three-week cycle until disease progression. Following progression, patients were administered a chemotherapy regimen consisting of oxaliplatin 85 mg/m^2 IV over 2 h on day 1 plus leucovorin 400 mg/m^2 IV over 2 h on day 1 plus 5-FU 400 mg/m^2 IV bolus on day 1, then 1,200 mg/m^2/day for 2 days (total 2,400 mg/m^2 over 46–48 h) continuous infusion, repeated every 2 weeks as second-line treatment. Patients received maintenance therapy with their latest regime until death as long as they tolerate.

After each chemotherapy session, patients received 60-min of local hyperthermia application and 60 min of hyperbaric oxygen therapy. For each hyperthermia session, OncoTherm EHY-3010 HT device (OncoTherm, Troisdorf, Germany) was used to gradually increase the temperature of the tumoral region to 45°C with a mobile electrode. Quamvis 320 hyperbaric oxygen chamber (OxyHealth, CA, USA) was used to produce an operating pressure of 1.5 atmospheres absolute (ATA) in each HBOT session.

Assessment of response

Assessment of treatment response was based on radiographic evaluations at the end of each 3-month period and was done by PET-CT. In patients with complete response based on PET-CT scan, confirmatory endoscopic evaluation was also done.

Statistical analysis

Data were analyzed using IBM SPSS Statistics version 21.0 software (SPSS Inc., Chicago, IL, USA). Descriptive data were presented in number (percentage), median (range), mean (95% confidence interval), where appropriate. The

time between the date of diagnosis and death from any cause was defined as overall survival. Progression-free survival was defined as the time frame between the date of diagnosis and death from any cause or progression. Patients without event at the last follow-up were censored. Kaplan–Meier analysis was used to estimate survival rates and intergroup comparisons were performed using log-rank test. Level of statistical significance was set at $P < 0.05$.

Results

Patient characteristics are shown in Table 1. Majority of the patients (75.0%) had metastatic disease and more than one-third had relatively poor performance status (ECOG status ≥2). In 22 patients (88.0%), PET-CT showed complete response at follow-up and this was confirmed by the endoscopic and histological absence of tumor (in blind biopsies) in all patients. In three patients, partial response could be achieved (12.0%). Seven patients received surgical treatment (29.2%). Three of them (12.5%) had surgery before chemotherapy and considered to be at advanced stage based on intraoperative or histopathological findings. The remaining four (16.7%) had surgery after complete response to chemotherapy.

Table 1: Patient characteristics

Characteristic	*n*=24
Age, year, median (range)	54 (32-76)
Male gender	14 (58.3%)
Disease extent	
Metastatic (stage IV)	18 (75.0%)
Locally advanced (stage III)	6 (25.0%)
ECOG status	
I-II	15 (62.5%)
III	9 (37.5%)
Histology	
Adenocarcinoma	9 (37.5%)
Signet ring cell carcinoma	15 (62.5%)
Radiotherapy	12 (50.0%)
Surgery	7 (29.2%)

Unless otherwise stated, data presented as *n* (%). ECOG=Eastern Cooperative Oncology Group

During the mean duration of follow-up of 23.9 ± 12.7 months (median 22.2, range 8.6–63.5 months), 9 patients died. Mean overall survival was 39.5 months (95% confidence interval [CI]: 28.1–51.0) and mean progression free survival was 36.5 months (95% CI: 25.7–47.2). Figure 1 shows Kaplan–Meier curves for overall survival and progression free survival.

Table 2 shows mean overall survival and mean progression-free survival by patient characteristics. None of the patient characteristics, including age, gender, disease extent, performance status, histology or additional treatments, had any effect on overall survival or progression free survival.

Table 2: Survival rates by patient characteristics

Characteristic	Mean OS Months (95% CI)	*P**	Mean PFS Months (95% CI)	*P**
All patients (*n*=24)	39.5 (28.1-51.0)		36.5 (25.7-47.2)	
Age				
≤Median (*n*=12)	41.7 (25.2-58.2)	0.735	39.3 (22.8-55.7)	0.701
>Median (*n*=12)	29.4 (24.4-34.4)		27.4 (22.1-32.8)	
Gender				
Male (*n*=14)	33.2 (25.9-40.5)	0.925	32.3 (24.3-40.3)	0.700
Female (*n*=10)	42.6 (22.6-62.6)		38.0 (20.4-55.6)	
Disease extent				
Metastatic (*n*=18)	35.7 (23.9-47.5)	0.318	32.3 (21.2-43.4)	0.204
Locally advanced (*n*=6)	41.3 (32.7-49.9)		40.9 (31.7-50.2)	
ECOG status				
I-II (*n*=15)	46.2 (31.5-60.9)	0.675	44.8 (30.9-58.6)	0.420
III (*n*=9)	31.9 (24.0-39.8)		29.1 (21.1-37.1)	
Histology				
Adenocarcinoma (*n*=9)	35.6 (26.8-44.5)	0.608	31.9 (22.3-41.5)	0.992
Signet ring cell carcinoma (*n*=15)	39.5 (25.2-53.9)		37.7 (23.4-52.0)	
Surgery				
Surgery (*n*=12)	39.9 (29.8-49.9)	0.331	39.8 (29.8-49.9)	0.220
No surgery (*n*=12)	36.7 (24.2-49.2)		32.9 (21.2-44.6)	
Radiotherapy				
Radiotherapy (*n*=7)	33.7 (28.2-39.2)	0.246	31.7 (25.6-37.8)	0.369
No radiotherapy (*n*=17)	35.3 (23.3-47.4)		33.3 (21.3-45.3)	

*Log-rank test

*Significance was set at $P < 0.05$. OS=overall survival; PFS=progression-free survival; ECOG=Eastern Cooperative Oncology Group

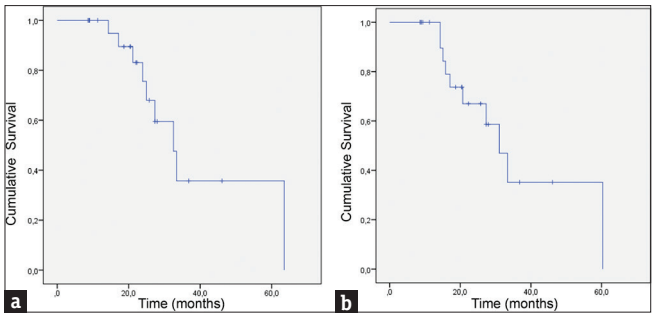

Figure 1: Kaplan–Meier curves for overall survival (a) and progression-free survival (b) – all patients. *P* values are calculated with log-rank test

During the study period, no problems were encountered due to fasting, hypoglycemia, ketogenic diet, hyperthermia, or hyperbaric oxygen therapy.

Discussion

This study integrated additional modalities targeting multiple susceptibilities of tumor cells into a chemotherapy schedule in patients with advanced gastric cancer and obtained promising results in terms of survival outcomes. To the best of our knowledge, this study is the first to examine the efficacy of a chemotherapy schedule administered in a metabolically supported fashion, together with ketogenic diet, hyperthermia, and HBOT, in patients with advanced gastric cancer.

A recent meta-analysis compared triplet versus doublet chemotherapy as a first-line treatment in patients with advanced esophagogastric cancer.[37] Triplet chemotherapy was associated with superior survival and response outcomes, despite increases in grade 3–4 thrombocytopenia, infection, and mucositis risks.[37] In that meta-analysis, reported overall survival rates ranged between 9.2 and 14.6 months in the arms of patients that received triplet combinations with taxane, platinum, and fluoropyrimidine. Among them, the largest V325 study reported 9.2 months of overall survival in the arm of docetaxel and cisplatin plus fluorouracil,[38] which is similar to the chemotherapy regimen administered in the present study. In addition, a recent study included advanced gastric cancer patients with good performance status (0–1) to test the efficacy and tolerability of docetaxel and cisplatin plus S-1 combination as a first-line chemotherapy and obtained median progression free survival and overall survival of 6.5 and 15.5 months, respectively.[39] In this study, a taxane, platinum, and fluoropyrimidine-based combination was administered as a first-line treatment to advanced gastric cancer patients with relatively poor outlook (75% having distant metastasis and more than one-third with ECOG PS ≥2) and encouraging survival outcomes were obtained (mean overall survival, 39.5 months; mean progression free survival 36.5 months) during a mean follow-up period of 2 years. However, median survival could not be reached since >60% of the patients were alive at the time of last evaluation. These promising findings may be attributed to the possible contribution of metabolically supported administration and additional modalities targeting multiple susceptibilities of the tumor cell included in the present study, which merit further investigation in large comparative trials.

To the best of our knowledge, only a few studies have reported on the use of MSCT in several malignancies: A retrospective clinical study and two case reports. A recent study in patients with unresectable ductal pancreatic adenocarcinoma examined the efficacy of standard gemcitabine-based and/or FOLFIRINOX protocol administered in a metabolically supported fashion and reported a median survival of 19.5 months for these patients with poor expected outcome.[17] FOLFOX6 regimen administered using MSCT approach in an elderly patient with locally advanced rectal cancer provided complete clinical and pathological response,[18] and an MSCT regimen combining docetaxel, doxorubicin, cyclophosphamide in a an overweight 29-year-old woman with stage IV (T4N3M1) triple-negative invasive ductal carcinoma of the breast provided complete clinical, radiological, and pathological response.[19]

Previous studies provided evidence on potential mechanisms through which metabolic support to chemotherapy may exert its beneficial effects. Both insulin itself and the resultant induced hypoglycemia seem to have role. Induced hypoglycemia targets the dysregulated metabolism and glucose dependency of the tumor cell.[13-16,40] Low availability of circulating glucose would pose an acute metabolic stress and probably improve cytotoxicity of the chemotherapeutic agent. Insulin itself has the potential to increase membrane permeability to chemotherapeutics, thereby increasing their availability for the tumor cell, through the formation of drug–insulin complexes.[41-45] In addition, number of insulin and insulin-like growth factor (IGF) receptors is higher on tumor cells when compared to healthy cells.[46,47] Reaction between insulin and these receptors has the potential to extend the S-phase and render cancer cells more susceptible to the cytotoxic effects of chemotherapeutics for longer periods,[48] while relatively sparing healthy cells, thereby improving safety and tolerability.

Ketogenic diet, another component of our combination treatment also targets metabolic dysregulation of tumor cells and possibly exerts its action through lowering the level of available circulating glucose. To date,

several preclinical studies and case reports provided support for its potential adjunctive use in the treatment of malignant conditions.[19,21-25,49-54] Hyperthermia, exploits heat sensitivity of cancer cells and causes direct cytotoxicity, and HBOT target 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 pro-oxidant chemotherapy and radiation therapies.[55] The synergism observed in various combination of these therapies (ketogenic diet, hyperthermia, HBOT) and their benefits in increasing the efficacy of conventional therapies have already been reported in a number of studies studying various malignant conditions.[15,19,24-29,35,56,57] Among them, the study by Ohguri *et al*. added hyperthermia and HBOT to carboplatin/paclitaxel chemotherapy in NSCLC patients with multiple pulmonary metastasis and obtained promising results (an objective response in almost two-thirds of the patients).[26] In addition, a recent study evaluated the effect of administration of all these three modalities along with MSCT in stage IV triple negative breast cancer patient with complete response.[19] This study also used all three modalities in addition to MSCT and targeted multiple vulnerabilities at metabolic, cellular and pharmacological level, which explains the high survival rates obtained.

Finding of this study, along with previous pre-clinical and clinical evidence, implies that adding modalities to complement conventional treatment may prove beneficial in many malignant conditions, provided that they target multiple vulnerabilities of tumor cells in an attempt to augment the efficacy and specificity of chemotherapeutic agents. Further research is warranted.

Retrospective design and the lack of a control group are the major limitations of this study. A randomized trial design would provide more robust evidence. In addition, relatively small sample size could have prevented to achieve power sufficient to detect survival differences between subgroups. Larger clinical studies with prospective design would further clarify the potential benefits of this treatment combination.

Conclusion

The combination treatment used, in this study (MSCT together with a ketogenic diet, hyperthermia and HBOT) is promising in the treatment of advanced gastric cancer. Further research and comparative clinical trials are warranted to support and standardize this novel treatment protocol.

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Conflicts of interest

There are no conflicts of interest.

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