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ORIGINAL ARTICLE

Supplemental home parenteral nutrition improved nutrition status with comparable quality of life in malnourished unresectable/metastatic gastric cancer receiving salvage chemotherapy

Cheng-Jen Ma[1,2] · Ching-Wen Huang[1,3] · Yung-Sung Yeh[1,4] · Hsiang-Lin Tsai[1,3] · Wei-Chih Su[1] · Tsung-Kun Chang[1] · Li-Chu Sun[5,6] · Ying-Ling Shih[5,6] · Fang-Jung Yu[7,8] · Deng-Chyang Wu[7,8] · Jaw-Yuan Wang[1,3,9,10,11,12,13]

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Abstract

Background Even with significant advances in surgical techniques and treatment, salvage chemotherapy remains the major treatment strategy for patients with unresectable or metastatic gastric cancer (GC). Practical and technical advances have simplified safe and convenient use of supplemental home parenteral nutrition (HPN). We aimed to clarify the role of HPN in patients with incurable GC undergoing salvage chemotherapy.

Methods We enrolled 25 patients with GC with a nutritional risk index (NRI) of ≦ 97.5 undergoing HPN. Their nutritional status, laboratory data, and quality of life (QoL) were analyzed using the Research and Treatment of Cancer quality of life questionnaire-C30 before and after HPN administration at 0.5, 1, 2, and 3 months. We enrolled 25 patients with an NRI of > 97.5 not undergoing HPN as the control group.

Results Total protein ($P = 0.008$), prealbumin ($P < 0.001$), and total cholesterol ($P = 0.023$) levels improved significantly after 0.5 months of HPN administration. The study group also demonstrated a marked improvement in nitrogen balance ($P = 0.004$) and prealbumin levels ($P < 0.012$) after 1 month. Gains in body weight after 1 month and body mass index after 2 months of HPN administration remained comparable with those of the control group. Global QoL scores were maintained and comparable with those of the control group.

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✉ Jaw-Yuan Wang
cy614112@ms14.hinet.net

[1] Division of Colorectal Surgery, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, No. 100, Tzyou 1st Road, Kaohsiung 807, Taiwan

[2] Division of General and Digestive Surgery, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan

[3] Department of Surgery, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

[4] Division of Trauma and Surgical Critical Care, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan

[5] Division of Nursing, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan

[6] Nutrition Therapy Team, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan

[7] Division of Gastroenterology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan

[8] Department of Internal Medicine, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

[9] Graduate Institute of Clinical Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

[10] Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

[11] Clinical Pharmacogenomics and Pharmacoproteinomics, College of Pharmacy, Taipei Medical University, Taipei, Taiwan

[12] Cohort Research Center, Kaohsiung Medical University, Kaohsiung, Taiwan

[13] Center for Cancer Research, Kaohsiung Medical University, Kaohsiung, Taiwan

Conclusions Supplemental HPN therapy for malnourished patients with unresectable or metastatic GC undergoing salvage chemotherapy is feasible and revealed marked improvement in nutritional status. Early HPN intervention should be considered an important part of palliative treatment for advanced GC.

Keywords Gastric cancer · Malnutrition · Home parenteral nutrition · Palliative care

Introduction

In Taiwan, gastric cancer (GC) is the sixth and fifth most common cancer in men and women, respectively, accounting for 3.8% of malignancies and 5.0% of malignancy-related deaths in 2013 [1]. Although significant advances have been made in surgical techniques and anticancer treatments, metastatic GC in a significant number of patients and locally advanced stage III GC in a proportion of patients remain unresectable. Therefore, salvage chemotherapy is a treatment option for palliative purposes.

Patients with unresectable or metastatic GC frequently experience malnutrition, which may be secondary to immune response and systemic inflammation, adverse events of chemotherapy, psychological factors, and gastrointestinal (GI) malfunction or bowel obstruction due to carcinomatosis. Furthermore, malnutrition, especially in the context of skeletal muscle wasting (sarcopenia), has been associated with an increased risk of developing intolerance to chemotherapy. The dosage of anticancer agents can cause increased toxicity, for which measures taken will potentially lead to dose reduction or treatment interruption, impaired quality of life (QoL), reduced performance status, and shortened survival time [2–4]. Malnutrition with poor or inadequate enteral nutrition (including oral nutrition supplements) in patients who lack adequate GI access or function indicates a need for parenteral nutrition (PN) [5]. PN can supplement daily nutritional needs that are unmet by enteral nutrition in patients with unresectable or metastatic GC and facilitate support or restoration of nutritional status. In patients with a terminal condition, PN may also prevent death from starvation and dehydration, for example, in patients with carcinomatosis with bowel obstruction.

Practical and technical advances have simplified the safe and convenient use of home parenteral nutrition (HPN). HPN can shorten in-hospital stays and increase the proportion of care in outpatient settings. In addition, HPN is suitable for the long-term care of patients. Therefore, it is a part of palliative care for patients with cancer and carries the potential to increase their survival and improve their QoL [6, 7].

Methods

The protocol was approved by the local ethics committees (KMUHIRB-2013-02-71) and was performed in accordance with the guidelines contained in the Declaration of Helsinki of 1975, as revised in 1996. Written informed consent was obtained from patients before any study activities were performed. The study was registered at www.clinicaltrials.gov (NCT03121807) under the trial name: Home Parenteral Nutrition for Malnourished Unresectable Stage IV Gastric Cancer (date of registration: 4 January 2017).

Patient eligibility

In this prospective observational study, patients (aged ≥ 20 years) with unresectable locally advanced stage III or metastatic (stage IV) GC who underwent salvage chemotherapy from October 2014 to January 2019 were screened for eligibility. A total of 25 patients with malnourishment and a nutritional risk index (NRI) of ≦ 97.5 comprised the study group, who received HPN. Exclusion criteria included the following laboratory results: absolute neutrophil count < $1.5 \times 10^3/\mu L$, platelet count < $60 \times 10^3/\mu L$, hemoglobin < 8.0 g/dL, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) > 3.0 × upper limit of normal (ULN) or AST and ALT > 5.0 × ULN in patients with liver metastasis, total bilirubin > 2.0 × ULN, and creatinine > 2.0 × ULN or calculated creatinine clearance < 60 mL/min. Additional exclusion criteria included the following: heart failure (New York Heart Association functional class > III) or stroke history; known diabetic ketoacidosis within 7 days before initiation of the study; body mass index (BMI) > 30 kg/m^2; drug abuse or chronic alcoholism; other life-threatening diseases; recent emergent surgery; ongoing infection; pregnancy or lactation; history of immunosuppressive therapy or recent immunological diseases; and participation in another clinical study with an investigational drug or an investigational medical device within 1 month of the initiation of the study.

For ethical reasons, we could not reject administering supplemental HPN to malnourished patients. Therefore, we enrolled 25 well-nourished patients with unresectable GC who also underwent salvage chemotherapy for comparison. No supplemental HPN was provided for these patients.

Intervention

For the study group, the PN regimen included a total caloric supplement of 910–1800 kcal/day, consisting of 33–60, 120–

240, and 30–60 g/day of amino acids, glucose, and lipids, respectively, according to patients' calorie-protein needs, which were estimated by dieticians of the nutrition therapy team based on oral intake or tubal feeding. The adequacy of supplemental HPN was assessed and the amount of supplemental HPN was adjusted every 2 weeks in accordance with the nitrogen balance of each patient. In addition, the regimen included electrolytes, microelements, and vitamins, dosed according to the nutritional status of the patient. PN was infused daily in an infusion time range between 18 and 24 h depending on the amount of infusion.

Nutritional, laboratory, and QoL measurements

NRI, body weight, and BMI measurements as well as blood tests were performed before HPN administration and at 0.5, 1, 2, and 3 months after HPN administration. Assessments included nitrogen balance, protein (albumin, prealbumin, total protein, and transferrin), lipids (triglycerides, cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL)), hematology (leukocyte count and hemoglobin), general chemistries (blood urea nitrogen (BUN) and creatinine), and liver function tests (total bilirubin, AST, and ALT). Nitrogen balance was calculated as daily nitrogen intake (including enteral nutrition and PN) minus daily nitrogen loss (24-hour urine urea nitrogen, urine nonurea nitrogen, and fecal and skin loss, which were assumed to be 4 g/day). QoL was assessed using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30 according to the same schedule.

Sample size

According to our preliminary results, nitrogen balance was − 1.92 g/day (SD, 4.48 g/day) for patients with NRI ≦ 97.5, with a correlation of 0.687 after HPN administration for 1 month. Using a two-sided sample size calculation before and after the study to detect a 2-g/day or greater difference to make nitrogen balance positive, the required sample size of the study group to obtain 80% power at alpha = 0.05 was 25. For comparison, we enrolled 25 patients with NRI > 97.5 as the control group, in which no HPN was administered, and the corresponding parameters were collected for comparison.

Statistical analysis

The results between groups were compared using the Mann–Whitney *U* test or Kruskal–Wallis test for categorical unpaired data. The Wilcoxon rank-sum test or Friedman test was used to analyze paired data. Fisher's exact test was used to compare dichotomous variables. Pearson's chi-square test was used to analyze nominal variables. McNemar's test was used to analyze paired categorical data. The means were compared using a two-sample test, analysis of variance (ANOVA), or linear regression, as appropriate. However, for all aforementioned inferential analysis methods, the center effect was not considered when comparing treatments. Therefore, ANOVA incorporating the center effect and Cochran–Mantel–Haenszel test stratified by the center effect were applied to replace the two-sample *t* test and Fisher's exact test. For efficacy analyses and some of the safety analyses (including laboratory data and vital sign data), analysis of covariance was applied when comparing treatment modes, with their respective baselines as covariates. Baseline data were defined as the data obtained before the first administration of treatment before surgery. This approach was based on the potential effect of baseline data on the endpoints. Endpoints were defined as the net change in post-treatment data from baseline data. Statistical analyses were performed using SPSS 20.0 (SPSS, Chicago, IL, USA). Results with $P < 0.05$ were considered statistically significant.

Results

Clinical characteristics at baseline and outcomes

In the study group, NRI improved and was higher than 97.5 in 8 out of 22 patients at 0.5 months, 3 out of 19 patients at 1 month, 6 out of 12 patients at 2 months, and 3 out of 7 patients at 3 months. Seven patients survived longer than 3 months, four patients survived longer than 4 months, and the remaining two survived longer than 5 months, including one patient whose NRI was higher than 97.5 at each time point after 0.5 month. Furthermore, median overall survival was significantly shorter in the study group than in the control group (2 vs. 19 months, 95% confidence interval (CI), 0.6–3.4 vs. 1.6–36.4, $P < 0.001$, HR = 4.39, 95% CI, 2.0–9.6, Fig. 1). The median HPN administration period was 135 days (range, 16–569 days). The study and control groups before HPN administration are compared in Table 1. Patients with malnourishment in the study group exhibited significantly lower serum levels of albumin ($P < 0.001$), prealbumin ($P < 0.001$), cholesterol ($P = 0.009$), HDL ($P = 0.049$), LDL ($P = 0.037$), hemoglobin ($P = 0.022$), and Na ($P = 0.003$) compared with those in the control group.

Differences in parameters after HPN intervention in the study group

Table 2 shows the differences in the parameters of patients in the study group after HPN intervention. Net change in body weight started to be positive at 1 month and BMI at 2 months although these changes were nonsignificant. In terms of lab assessments, albumin did not change significantly; however,

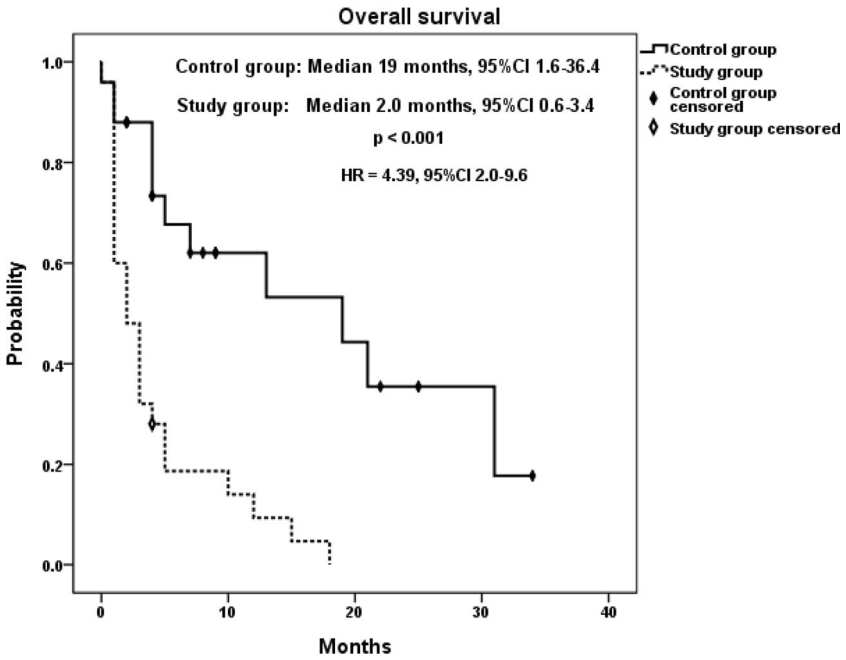

Fig. 1 Median overall survival

Table 1 Comparison of study group before home parenteral nutrition with control group (baseline)

	Study group NRI ≦ 97.5 (N = 25)	Control group NRI > 97.5 (N = 25)	P value
Sex			
Male/female	14/11	17/8	0.280
Age/median (years)	35–88/68	47–81/68	0.777
Nitrogen balance (g/day)	− 2.25 ± 5.88	− 1.78 ± 4.90	0.774
NRI	90.5 ± 6.4	106.5 ± 8.9	< 0.001
Body weight (kg)	51.66 ± 10.53	57.00 ± 9.75	0.069
BMI (kg/m^2)	20.1 ± 3.6	22 ± 3.5	0.070
Albumin (g/dL)	3.29 ± 0.44	3.99 ± 0.38	< 0.001
Pre-albumin (mg/dL)	13.08 ± 5.72	19.60 ± 5.97	< 0.001
Total protein (g/dL)	6.02 ± 0.71	6.37 ± 0.78	0.099
Triglyceride (mg/dL)	92.92 ± 53.88	87.12 ± 31.44	0.644
Cholesterol (mg/dL)	129.96 ± 34.50	155.44 ± 31.77	0.009
HDL (mg/dL)	37.24 ± 14.03	44.81 ± 12.50	0.049
LDL (mg/dL)	73.31 ± 29.78	90.73 ± 27.62	0.037
Transferrin (mg/dL)	188.64 ± 55.58	213.88 ± 42.93	0.079
Leukocyte (10^3/μL)	6.11 ± 2.49	6.10 ± 2.61	0.989
Hemoglobin (g/dL)	10.76 ± 1.41	11.66 ± 1.27	0.022
BUN (mg/dL)	16.41 ± 10.48	14.88 ± 8.00	0.564
Creatinine (mg/dL)	0.84 ± 0.30	0.83 ± 0.19	0.912
Total bilirubin (mg/dL)	0.70 ± 0.46	0.64 ± 0.26	0.550
AST (U/L)	28.92 ± 11.35	27.72 ± 10.00	0.693
ALT (U/L)	21.36 ± 11.47	19.36 ± 7.73	0.473
UICC stage			
III	10 (40%)	9 (36%)	0.771
IV	15 (60%)	16 (64%)	
ECOG			
1	11 (44%)	14 (56%)	0.396
2	14 (56%)	11 (44%)	

NRI, nutrition risk index; *BMI*, body mass index; *HDL*, **high-density lipoprotein;** *LDL*, **low-density lipoprotein;** *BUN*, blood urine nitrogen; *AST*, aspartate aminotransferase; *ALT*, alanine aminotransferase; *UICC*, Union of International Cancer Control; *ECOG*, Eastern Cooperative Oncology Group

Table 2 Differences using paired *t* test of parameters between before and after home parenteral nutrition in study group

	0.5 month ($N = 22$) M2–M1	*P* value	1.0 month ($N = 19$) M3–M1	*P* value	2.0 months ($N = 12$) M4–M1	*P* value	3.0 months ($N = 7$) M5–M1	*P* value
Nitrogen balance (g/day)	− 0.73 ± 3.45	0.568	5.17 ± 5.44	0.004	1.50 ± 5.25	0.478	2.44 ± 1.16	0.207
NRI	2.7 ± 7.4	0.113	− 1.1 ± 6.7	0.480	3.7 ± 13.2	0.355	2.8 ± 8.9	0.399
Body weight (kg)	− 1.14 ± 4.14	0.212	4.13 ± 25.54	0.490	1.93 ± 5.24	0.227	3.34 ± 4.72	0.110
BMI (kg/m^2)	− 0.4 ± 1.7	0.285	− 0.4 ± 2.0	0.422	0.9 ± 2.4	0.248	1.3 ± 1.8	0.105
Albumin (g/dL)	0.08 ± 0.50	0.466	− 0.09 ± 0.44	0.384	0.00 ± 0.67	0.987	− 0.03 ± 0.51	0.894
Pre-albumin (mg/dL)	4.80 ± 5.12	< 0.001	3.01 ± 4.55	0.012	5.24 ± 7.88	0.065	3.44 ± 7.02	0.208
Total protein (g/dL)	0.62 ± 1.02	0.008	0.19 ± 0.67	0.233	0.50 ± 0.90	0.096	0.13 ± 0.72	0.638
Triglyceride (mg/dL)	9.48 ± 54.79	0.416	5.22 ± 32.89	0.510	37.08 ± 46.07	0.018	25.38 ± 34.14	0.083
Cholesterol (mg/dL)	13.13 ± 25.78	0.023	0.39 ± 30.63	0.958	6.92 ± 31.04	0.456	1.25 ± 34.45	0.921
HDL (mg/dL)	− 4.11 ± 12.05	0.124	− 5.95 ± 11.73	0.061	− 5.46 ± 15.46	0.247	− 1.46 ± 12.02	0.741
LDL (mg/dL)	13.05 ± 25.11	0.024	3.97 ± 31.48	0.610	11.44 ± 23.26	0.116	1.81 ± 32.98	0.881
Transferrin (mg/dL)	18.22 ± 42.94	0.054	2.56 ± 28.38	0.707	7.91 ± 76.09	0.737	8.50 ± 88.66	0.794
Leukocyte ($10^3/\mu L$)	1.33 ± 3.46	0.073	0.37 ± 2.85	0.580	0.34 ± 3.98	0.770	0.83 ± 4.46	0.616
Hemoglobin (g/dL)	− 0.06 ± 1.23	0.819	− 0.64 ± 1.57	0.091	− 0.68 ± 1.13	0.062	− 0.73 ± 2.00	0.340
BUN (mg/dL)	1.25 ± 12.27	0.655	0.08 ± 9.14	0.970	1.58 ± 7.59	0.487	3.53 ± 4.04	0.043
Creatinine (mg/dL)	0.04 ± 0.32	0.604	− 0.05 ± 0.19	0.272	− 0.07 ± 0.15	0.144	− 0.09 ± 0.12	0.087
Total bilirubin (mg/dL)	0.75 ± 1.54	0.030	0.36 ± 1.40	0.288	0.15 ± 0.51	0.326	0.14 ± 0.77	0.630
AST (U/L)	1.38 ± 12.66	0.600	2.78 ± 18.69	0.537	0.75 ± 11.88	0.831	8.13 ± 9.36	0.044
ALT (U/L)	0.88 ± 12.47	0.734	4.44 ± 19.53	0.348	4.83 ± 18.96	0.396	5.38 ± 8.26	0.108

M1, mean of before intervention; *M2*, mean of 0.5 month after intervention; *M3*, mean of 1.0 month after intervention; *M4*, mean of 2.0 months after intervention; *M5*, mean of 3.0 months after intervention; *NRI*, nutrition risk index; *BMI*, body mass index; *HDL*, **high-density lipoprotein;** *LDL*, **low-density lipoprotein;** *BUN*, blood urine nitrogen; *AST*, aspartate aminotransferase; *ALT*, alanine aminotransferase

prealbumin, total protein, triglycerides, cholesterol, LDL, and transferrin levels increased throughout the study period. Prealbumin increased significantly at 0.5 month ($P < 0.001$) and 1 month ($P = 0.012$); total protein ($P = 0.008$), cholesterol ($P = 0.023$), and LDL ($P = 0.024$) increased significantly at 0.5 month; and triglycerides increased significantly at 2 months ($P = 0.018$). Positive changes in nitrogen balance began at 1 month, and the difference was significant ($P = 0.004$). Total bilirubin was elevated significantly at 0.5 month ($P = 0.030$) although the level was generally less than 2.0 mg/dL. AST and ALT were elevated after HPN administration, but the levels remained less than ULN.

Differences between the study group after HPN intervention and control group

Table 3 demonstrates differences in parameters between the study and control groups at different observation times. NRI in the study group improved especially at 2 and 3 months but was still worse than that in the control group ($P = 0.004$ and 0.010, respectively). Body weight, BMI, prealbumin, cholesterol, HDL, and LDL of the study group were comparable with those of the control group after 1 month ($P = 0.849$), 2 months ($P = 0.077$), 1 month ($P = 0.051$), 0.5 month ($P = 0.352$), 2 months ($P = 0.129$), and 0.5 month ($P = 0.749$), respectively. Nitrogen balance was significantly better in the study group than in the control group at 1 month ($P = 0.011$) and 3 months ($P = 0.023$).

QoL at baseline

Differences in scale scores of EROTC QLQ-C30 between the study group before treatment and control group are summarized in Table 4. At baseline, compared with those in the control group, the scores of physical functioning (PF) ($P < 0.032$), fatigue (FA) ($P = 0.013$), and appetite loss (AP) ($P = 0.004$) were significantly worse in the study group, but the global QoL scores did not differ ($P = 0.087$) between the two groups before HPN treatment.

Differences in QoL scores after HPN intervention in the study group

Changes in EORTC scores after treatment initiation are shown in Table 5. For PF, the score decreased significantly at 0.5 month ($P = 0.016$), 1 month ($P = 0.048$), and 3 months ($P < 0.001$). The score for role functioning (RF) decreased significantly at 0.5 month ($P < 0.001$), 1 month ($P = 0.001$), 2 months ($P = 0.022$), and 3 months ($P = 0.006$) after HPN treatment. Both emotional functioning (EF) and social functioning (SF) scores declined significantly only at 3 months ($P = 0.042$ and 0.033, respectively). The scores of FA ($P = 0.010$) and financial difficulties (FI) ($P = 0.048$) increased significantly at 3 months, whereas dyspnea (DY) scores increased significantly at 2 months ($P = 0.028$). No significant change in global QoL scores was observed during the study period.

Differences in QoL scores between the study group after HPN intervention and the control group

Compared with the control group at different time points after HPN intervention, the scores of PF, RF, and SF were significantly impaired in the study group throughout the study period, except for the SF scores at 2 months ($P = 0.091$). The FA score was significantly worse in the study group than in the control group throughout the study period ($P = 0.001$, 0.011, 0.007, and 0.002 at 0.5, 1, 2, and 3 months, respectively). Compared with those of the control group, the dyspnea scores of the study group were significantly worse at 2 months ($P = 0.016$) and 3 months ($P = 0.023$), and AP score was significantly worse at 3 months ($P = 0.035$, Table 6).

Discussion

Malnutrition is a condition frequently encountered in patients with cancer, especially in those with GC. Symptoms caused by GC itself can include anorexia, nausea, vomiting, fatigue, pain, gastric outlet obstruction, and impaired food intake. Moreover, the toxicities of anticancer drugs, including mucositis, constipation, and diarrhea, can exacerbate these symptoms and further reduce oral feeding. This is a vicious circle and, with a long-term lack of enteral stimulation by food or tube feeding, malnutrition results in small intestine mucosal atrophy, reduction of mucosal cell proliferation, and corruption of intestinal mucosal barrier function [8]. In addition, the immune response to cancer and inflammatory cytokines released by cancer cells results in systemic inflammation [9, 10], which together with the cancer itself, increases metabolism and energy and protein needs in turn. Essentially, psychological stress, depression, and decreased physical activity because of (or leading to) reduced performance status can also influence food intake. When nutrient intake fails to meet protein and energy needs in the context of elevated metabolic rate, depletion of body reserves results. Decline in skeletal muscle mass, function, and quality, critical for patients with cancer, eventually result in sarcopenia. Sarcopenia not only further limits physical activity, but also adversely impacts the risk of toxicity of anticancer drugs [11–13] and is associated with shorter survival, as demonstrated by rapidly accumulating evidence [14–18]. These findings are consistent with the results of the current study, in which malnourished patients had short median overall survival; this demonstrated that malnutrition may reflect not only disease severity but also disease prognosis. NRI is a nutritional screening tool composed of the two

Table 3 Differences between study group after treatment and control group

	Control group NRI > 97.5 (*N* = 25)	Study group 0.5 month (*N* = 22)	*P* value	Study group 1.0 month (*N* = 19)	*P* value	Study group 2.0 months (*N* = 12)	*P* value	Study group 3.0 months (*N* = 7)	*P* value
Nitrogen balance (g/day)	− 1.78 ± 4.90	− 1.49 ± 5.77	0.889	2.50 ± 4.44	0.011	1.41 ± 7.23	0.188	6.94 ± 4.21	0.023
NRI	106.5 ± 8.9	93.8 ± 8.3	< 0.001	91.1 ± 6.8	< 0.001	96.4 ± 10.6	0.004	96.6 ± 8.9	0.010
Body weight (kg)	57.00 ± 9.75	50.03 ± 9.90	0.019	55.82 ± 28.88	0.849	50.53 ± 9.99	0.069	52.56 ± 12.70	0.326
BMI (kg/m^2)	22.0 ± 3.5	19.4 ± 3.1	0.012	19.6 ± 3.3	0.027	19.7 ± 3.6	0.077	20.3 ± 3.5	0.257
Albumin (g/dL)	3.99 ± 0.38	3.38 ± 0.50	< 0.001	3.26 ± 0.50	< 0.001	3.42 ± 0.47	< 0.001	3.42 ± 0.38	0.001
Pre-albumin (mg/dL)	19.60 ± 5.97	17.89 ± 8.09	0.406	16.09 ± 5.12	0.051	17.04 ± 7.99	0.307	17.15 ± 5.71	0.316
Total protein (g/dL)	6.37 ± 0.78	6.64 ± 1.02	0.309	6.31 ± 0.79	0.791	6.54 ± 0.72	0.551	6.40 ± 0.75	0.925
Triglyceride (mg/dL)	87.12 ± 31.44	103.35 ± 46.51	0.160	93.33 ± 48.44	0.613	108.83 ± 31.99	0.059	25.38 ± 35.68	0.779
Cholesterol (mg/dL)	155.44 ± 31.77	145.74 ± 39.49	0.352	140.50 ± 27.63	0.116	134.83 ± 32.60	0.076	134.38 ± 34.45	0.123
HDL (mg/dL)	44.81 ± 12.50	34.34 ± 14.85	0.012	35.41 ± 11.24	0.019	37.60 ± 14.62	0.129	40.19 ± 17.17	0.412
LDL (mg/dL)	90.73 ± 27.62	87.68 ± 37.32	0.749	84.88 ± 25.13	0.489	78.84 ± 19.53	0.190	75.93 ± 25.06	0.188
Transferrin (mg/dL)	213.88 ± 42.93	215.04 ± 63.59	0.941	205.00 ± 46.53	0.522	213.64 ± 77.69	0.990	212.38 ± 69.93	0.942
Leukocyte (10^3/μL)	6.10 ± 2.61	7.41 ± 3.68	0.154	6.28 ± 3.22	0.838	5.92 ± 3.16	0.858	6.22 ± 2.88	0.616
Hemoglobin (g/dL)	11.66 ± 1.27	10.78 ± 1.52	0.032	10.03 ± 1.56	< 0.001	9.91 ± 1.42	0.001	9.89 ± 1.27	0.002
BUN (mg/dL)	14.88 ± 8.00	18.50 ± 12.86	0.243	16.18 ± 7.76	0.596	15.93 ± 6.46	0.696	16.34 ± 8.18	0.659
Creatinine (mg/dL)	0.83 ± 0.19	0.89 ± 0.46	0.557	0.79 ± 0.27	0.581	0.67 ± 0.20	0.032	0.66 ± 0.28	0.068
Total bilirubin (mg/dL)	0.64 ± 0.26	1.44 ± 1.88	0.041	0.96 ± 1.39	0.265	0.72 ± 0.43	0.455	0.80 ± 0.66	0.318
AST (U/L)	27.72 ± 10.00	29.83 ± 14.51	0.554	31.39 ± 15.03	0.342	29.50 ± 10.05	0.616	36.88 ± 11.28	0.036
ALT (U/L)	19.36 ± 7.73	21.83 ± 8.46	0.290	25.61 ± 16.67	0.107	26.17 ± 16.45	0.093	26.88 ± 12.09	0.046

NRI, nutrition risk index; *BMI*, body mass index; *HDL*, **high-density lipoprotein;** *LDL*, **low-density lipoprotein;** *BUN*, blood urine nitrogen; *AST*, aspartate aminotransferase; *ALT*, alanine aminotransferase

Table 4 Differences of scale scores of EORTC QLQ-C30 between study group before treatment and control group

	Study group before treatment NRI ≦ 97.5 ($N = 25$)	Control group at baseline NRI > 97.5 ($N = 25$)	P value
Functional scales			
PF	54.12 ± 22.81	67.68 ± 20.60	0.032
RF	42.68 ± 26.08	56.00 ± 26.91	0.082
EF	70.04 ± 22.57	76.12 ± 19.15	0.310
CF	80.60 ± 24.83	80.04 ± 20.94	0.932
SF	48.76 ± 23.74	61.44 ± 21.00	0.051
Symptom scales			
FA	56.44 ± 20.74	40.44 ± 23.27	0.013
NV	34.00 ± 27.40	29.28 ± 24.25	0.522
PA	35.32 ± 31.73	34.64 ± 27.25	0.936
DY	8.00 ± 19.95	3.96 ± 10.94	0.379
SL	30.56 ± 30.34	31.88 ± 22.62	0.862
AP	58.76 ± 27.82	35.96 ± 25.46	0.004
CO	30.60 ± 28.81	22.52 ± 24.90	0.294
DI	13.24 ± 23.49	10.56 ± 24.90	0.638
FI	41.24 ± 27.82	41.20 ± 22.29	0.996
Global health status			
QoL	30.64 ± 15.85	40.92 ± 24.74	0.087

EROTC, The European Organization for Research and Treatment of Cancer; *QLQ*, quality of life questionnaire; *PF*, **physical functioning;** *RF*, role functioning**;** *EF*, emotional functioning; *CF*, cognitive functioning; *SF*, social functioning; *FA*, fatigue; *NV*, nausea and vomiting; *PA*, pain; *DY*, dyspnea; *SL*, insomnia; *AP*, appetite loss; *CO*, constipation; *DI*, diarrhea; *FI*, financial difficulties; *QoL*, quality of life

variables of body weight loss and serum albumin level that is simple and easily practiced, especially for outpatient visits. However, even with its lower sensitivity and specificity compared with that of the patient-generated subjective global assessment (PG-SGA), both are predictive of outcomes [19].

PN is a solution for patients whose enteral nutrition does not satisfy their daily nutrition requirements. For patients with unresectable or metastatic GC, HPN should be considered because inadequate food intake and anticancer therapy may last for a protracted time. HPN reduces hospital stay and financial costs and provides additional time to these patients to be cared for in their familiar home environments. For appropriately selected patients with advanced or terminal cancer in the context of a nonfunctioning gut or malignant bowel obstruction, HPN, as part of a palliative treatment, can also prevent death from starvation and dehydration. In the appropriate setting, such carcinomatosis and small bowel obstruction, can offer the potential to prolong survival and improve QoL.

In the present study, the gains in body weight after 1 month and in BMI after 2 months following HPN administration in the study group remained comparable with those in the control group. Prealbumin, cholesterol, and LDL which were significantly lower in the study group before HPN administration, increased significantly at 0.5 month and were comparable with those in the control group after treatment. Although NRI improved, the difference was not significant. However, negative nitrogen balance at baseline notably became positive after 1 month in the study group. Eventually, nitrogen balance was significantly higher in the study group than in the control group at 3 months. Improvement in nutritional status was not reflected by the albumin level in the 3-month observation time. This is consistent with the albumin half-life of 21 days, which implies that 100 days are required to reach a new steady level [20]. Consistently, low levels of hemoglobin in the study group corresponded with more serious GC, which directly resulted in bleeding and consequent chronic anemia, as well as serious malnutrition. Although total bilirubin, AST, and BUN were elevated slightly in the study group, the values remained less than ULN. Long-term HPN was notably not associated with any deterioration in liver or kidney functions.

Before HPN was introduced, the baseline score of PF was significantly lower, and FA and AP scores were significantly more severe in the study group than in the control group. Appetite increased after 0.5 month of HPN administration, whereas FA did not change. The PF and RF scores were impaired as the disease progressed. The EF and SF scores declined significantly at 3 months and symptoms of FA and DY deteriorated at the end of their life. The FI scores in the study group were comparable with those in the control group. This may partially result from fewer in-hospital costs and partially because the Taiwan national health insurance system covers almost all treatment expense for patients with cancer. Deterioration of EORTC symptom scales in the study group is mainly related to progression of disease at the end of life, whereas metabolic and infectious complications are the most commonly encountered side effects of HPN administration. Despite the adverse changes mentioned, the global QoL score was maintained and was comparable with that of the patients in the control group.

HPN administration in patients with incurable cancer and life expectancy shorter than 2–3 months has been debated [21, 22]. However, the World Health Organization (WHO) defined palliative care as "an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment, and treatment of pain and other problems—physical, psychosocial, and spiritual" [23]. Moreover, PN has become an integral part of palliative care for patients with cancer [6]. Recent studies have demonstrated significant improvements in global the QoL and nutritional status of patients with cancer after 4 weeks of HPN administration [24–26]. Cotogni et al. also reported that global QoL, PF, RF, EF, FA, and AP exhibited a significant favorable trend in patients with advanced cancer receiving oncological treatment with a median

Table 5 Differences of scale scores of EROTC QLQ-C30 using paired t-test between before and after intervention in study group

	0.5 month ($N = 22$) M2–M1	*P* value	1.0 month ($N = 19$) M3–M1	*P* value	2.0 months ($N = 12$) M4–M1	*P* value	3.0 months ($N = 7$) M5–M1	*P* value
Functional scales								
PF	− 11.71 ± 22.06	0.016	− 11.11 ± 22.09	0.048	− 10.17 ± 21.75	0.134	− 32.38 ± 11.45	< 0.001
RF	− 20.29 ± 21.55	< 0.001	− 21.33 ± 22.84	0.001	− 22.25 ± 28.80	0.022	− 29.25 ± 21.46	0.006
EF	− 3.58 ± 15.62	0.273	1.39 ± 17.06	0.734	2.75 ± 14.65	0.529	− 12.25 ± 13.95	0.042
CF	− 4.79 ± 16.60	0.171	− 2.83 ± 18.30	0.520	4.08 ± 16.18	0.401	− 6.38 ± 23.23	0.463
SF	− 4.25 ± 22.98	0.374	− 3.78 ± 20.66	0.449	− 5.67 ± 11.07	0.104	− 17.00 ± 18.17	0.033
Symptom scales								
FA	5.17 ± 18.62	0.187	5.00 ± 22.86	0.366	11.17 ± 25.43	0.156	23.88 ± 19.37	0.010
NV	− 4.88 ± 54.79	0.337	− 10.22 ± 28.72	0.149	− 5.42 ± 32.17	0.571	− 10.25 ± 21.69	0.223
PA	− 0.75 ± 19.61	0.853	4.56 ± 19.63	0.339	5.58 ± 18.10	0.308	16.63 ± 25.33	0.106
DY	4.13 ± 20.42	0.333	5.44 ± 20.52	0.276	19.42 ± 26.49	0.028	20.88 ± 30.66	0.096
SL	4.17 ± 24.80	0.419	3.78 ± 27.95	0.574	2.83 ± 39.05	0.806	4.25 ± 33.26	0.728
AP	− 6.96 ± 19.60	0.095	− 7.44 ± 33.55	0.360	− 8.33 ± 28.97	0.341	8.38 ± 29.70	0.451
CO	− 2.75 ± 32.60	0.683	5.67 ± 30.89	0.447	13.92 ± 36.03	0.208	4.13 ± 21.15	0.598
DI	− 1.38 ± 11.84	0.575	0.06 ± 16.13	0.989	0.00 ± 19.90	1.000	8.38 ± 15.51	0.171
FI	6.92 ± 24.27	0.176	11.17 ± 28.29	0.112	2.83 ± 9.81	0.339	21.13 ± 25.03	0.048
Global health status								
QoL	4.21 ± 16.98	0.237	0.06 ± 18.89	0.990	2.00 ± 17.70	0.703	− 3.25 ± 23.19	0.704

M1, mean of before intervention; *M2*, mean of 0.5 month after intervention; *M3*, mean of 1.0 month after intervention; *M4*, mean of 2.0 months after intervention; *M5*, mean of 3.0 months after intervention; *EROTC*, The European Organization for Research and Treatment of Cancer; *QLQ*, quality of life questionnaire; *PF*, **physical functioning**; *RF*, role functioning**;** *EF*, emotional functioning; *CF*, cognitive functioning; *SF*, social functioning; *FA*, fatigue; *NV*, nausea and vomiting; *PA*, pain; *DY*, dyspnea; *SL*, insomnia; *AP*, appetite loss; *CO*, constipation; *DI*, diarrhea; *FI*, financial difficulties; *QoL*, quality of Life

Table 6 Differences of scale scores of EROTC QLQ-C30 between study group after treatment and control group

	Control group NRI > 97.5 ($N = 25$)	Study group 0.5 month ($N = 22$)	*P* value	Study group 1.0 month ($N = 19$)	*P* value	Study group 2.0 months ($N = 12$)	*P* value	Study group 3.0 months ($N = 7$)	*P* value
Functional scales									
PF	67.68 ± 20.60	41.63 ± 26.46	< 0.001	41.89 ± 25.99	0.001	40.50 ± 25.75	0.001	29.38 ± 20.78	< 0.001
RF	56.00 ± 26.91	21.38 ± 19.88	< 0.001	20.28 ± 23.26	< 0.0001	20.75 ± 21.44	< 0.001	22.75 ± 19.70	0.003
EF	76.12 ± 19.15	66.58 ± 24.65	0.136	72.67 ± 21.36	0.581	76.33 ± 19.75	0.975	60.63 ± 23.96	0.070
CF	80.04 ± 20.94	75.00 ± 25.91	0.457	79.50 ± 23.90	0.938	81.83 ± 27.92	0.828	81.13 ± 10.51	0.890
SF	61.44 ± 21.00	43.75 ± 23.17	0.007	47.22 ± 20.27	0.032	46.67 ± 20.87	0.091	43.63 ± 15.57	0.035
Symptom scales									
FA	40.44 ± 23.27	62.58 ± 22.36	0.001	60.56 ± 25.80	0.011	64.83 ± 26.89	0.007	69.63 ± 14.35	0.002
NV	29.28 ± 24.25	29.17 ± 25.65	0.987	19.44 ± 23.05	0.188	26.50 ± 28.01	0.758	23.00 ± 21.72	0.519
PA	34.64 ± 27.25	34.67 ± 31.50	0.997	37.00 ± 32.67	0.798	36.17 ± 34.03	0.884	37.50 ± 23.25	0.791
DY	3.96 ± 10.94	11.08 ± 21.25	0.144	11.00 ± 16.00	0.094	19.42 ± 26.49	0.016	20.88 ± 30.66	0.023
SL	31.88 ± 22.62	34.63 ± 33.35	0.737	33.33 ± 32.44	0.863	33.33 ± 34.90	0.879	33.38 ± 31.02	0.883
AP	35.96 ± 25.46	51.46 ± 34.13	0.077	46.33 ± 36.50	0.278	47.25 ± 36.22	0.280	58.38 ± 23.79	0.035
CO	22.52 ± 24.90	29.13 ± 26.68	0.375	33.33 ± 28.15	0.191	33.25 ± 31.85	0.270	29.00 ± 33.01	0.558
DI	10.56 ± 24.90	11.04 ± 23.33	0.933	12.94 ± 28.34	0.726	16.58 ± 30.10	0.426	16.63 ± 25.23	0.421
FI	41.20 ± 22.29	48.50 ± 26.15	0.298	49.94 ± 20.88	0.200	41.50 ± 25.27	0.971	50.00 ± 18.17	0.320
Global health status									
QoL	40.92 ± 24.74	34.75 ± 16.89	0.315	32.44 ± 19.17	0.232	36.75 ± 15.67	0.598	38.50 ± 23.10	0.809

EROTC, The European Organization for Research and Treatment of Cancer; *QLQ*, quality of life questionnaire; *PF*, **physical functioning;** RF, role functioning**;** EF, emotional functioning; *CF*, cognitive functioning; *SF*, social functioning, *FA*, fatigue; *NV*, nausea and vomiting; *PA*, pain; *DY*, dyspnea; *SL*, insomnia; *AP*, appetite loss; *CO*, constipation; *DI*, diarrhea; *FI*, financial difficulties; *QoL*, quality of life

survival of 4.7 months. These results were consistent with those of a study conducted by Vashi et al. [27], which demonstrated that HPN administration was positively associated with improved QoL and nutritional status in patients with advanced cancer with compromised enteral intake and malnutrition. Furthermore, the greatest benefit was observed in patients with at least 3 months of HPN administration; however, significant improvement was also observed in those receiving HPN for 1 or 2 months. Although it is not demonstrated in the current study, Chermesh et al. concluded that HPN administration prevents death from starvation in patients with incurable cancer without oral intake and prolongs survival [28]. Moreover, HPN administration does not deteriorate QoL among caregivers [29]. Therefore, HPN administration meets the WHO definition and can be a critical, integral part of palliative care.

This study had several limitations. First, this was an observational prospective study with a small number of participants, and it may not have sufficient power to draw definite conclusions. However, performing a randomized trial is challenging because it involves including patients with malnourishment in the control group, which is unacceptable for ethical reasons. Second, the appropriateness of offering HPN to patients who are not expected to live longer than 2–3 months can be debated. However, recent evidence has demonstrated positive results of HPN in certain patients with terminal cancer. As such, HPN meets the WHO definition of palliative care.

Conclusion

Supplemental HPN administration had a positive impact on nutritional status and QoL in patients with malnourishment and incurable GC shortly after the initiation of treatment, despite being a small-sample study with limitations. Supplemental HPN was well tolerated, with no liver or kidney damage and can be reasonably included as an integral part of palliative care for appropriately chosen patients with terminal cancer with malnutrition. Early HPN intervention is imperative for malnourished patients with unresectable or metastatic GC undergoing salvage chemotherapy.

Authors' contributions C.J. Ma conducted the treatment, interpreted the final results, and drafted the manuscript. C.W. Huang and Y.S. Yeh collected data. H.L. Tsai, W.C. Su, and T.K. Chang participated in data analysis. L.C. Sun and Y.L. Shih assisted in treatment. F.J. Yu and D.C. Wu assisted in data interpretation. J.Y. Wang was responsible for study design and coordination. All authors read and approved the final manuscript.

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Availability of data and materials The data and materials analyzed in the current study are available from the corresponding author on reasonable requests.

Compliance with Ethical Standards

Conflict of interests The authors declare that they have no conflict of interest.

Ethical approval The protocol was approved by the local ethics committees (KMUHIRB-2013-02-71) and was performed in accordance with Declaration of Helsinki of 1975, as revised in 1996.

Consent to participate Written informed consent was obtained from patients before any study activities were performed.

Consent for publish Not applicable.

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