



Original/Cáncer

## Role of parenteral nutrition in oncologic patients with intestinal occlusion and peritoneal carcinomatosis

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### Abstract

**Introduction and aims:** the precise role of parenteral nutrition in the management of oncologic patients with intestinal occlusion is not well defined yet. We aimed to identify the effects of parenteral nutrition in these patients regarding prognosis.

**Material and methods:** 55 patients with intestinal occlusion and peritoneal carcinomatosis were included. Parenteral nutrition aimed at 20-35 kcal/Kg/day, and 1.0 g/kg/day of amino-acids. Weight, body mass index, type of tumor, type of chemotherapy, and ECOG among others were recorded and analyzed.

**Results:** 69.1% of the patients had gastrointestinal tumors, 18.2% gynecologic and 12.7% others. Age was 60 ± 13y, baseline ECOG 1.5 ± 0.5 and body mass index 21.6 ± 4.3. Malnutrition was present in 85%. Survival from the start of parenteral nutrition was not significant when considering baseline ECOG (log rank = 0.593, p = 0.743), previous lines of chemotherapy (log rank = 2.117, p = 0.548), baseline BMI (log rank = 2.686, p = 0.261), or type of tumor (log rank = 2.066, p = 0.356). Survival in patients who received home parenteral nutrition after hospital discharge was higher than those who stayed in-hospital (log rank = 7.090, p = 0.008). Survival in patients who started chemotherapy during or after parenteral nutrition was higher than those who did not so (log rank = 17.316, p < 0.001). A total of 3.6% of patients presented catheter related infection without affecting survival (log rank = 0.061, p = 0.804).

**Conclusions:** Parenteral nutrition in patients with advanced cancer and intestinal occlusion is safe, and in tho-

### PAPEL DE LA NUTRICIÓN PARENTERAL EN PACIENTES ONCOLÓGICOS CON OCLUSIÓN INTESTINAL Y CARCINOMATOSIS PERITONEAL

#### Resumen

**Introducción y objetivos:** el papel preciso de la nutrición parenteral en el manejo de los pacientes oncológicos con obstrucción intestinal no está bien definido todavía. El objetivo del presente trabajo es evaluar los efectos de la nutrición parenteral en este tipo de pacientes en cuanto al pronóstico.

**Material y métodos:** fueron incluidos 55 pacientes con obstrucción intestinal y carcinomatosis peritoneal. La nutrición parenteral proporcionó 20-35 kcal/Kg/día y 1.0 g/kg/día de aminoácidos. El peso, el IMC, el tipo de tumor, el tipo de quimioterapia recibida y el ECOG, entre otras variables, fueron recogidas y analizadas.

**Resultados:** un 69,1% de los pacientes presentaban tumores gastrointestinales, un 18,2% ginecológicos y otros tumores el 12,7% restante. La edad media fue de 60 ± 13 años, con un ECOG basal de 1,5 ± 0,5 y un IMC de 21,6 ± 4,3. La presencia de malnutrición fue de un 85%. La supervivencia desde el inicio de la nutrición parenteral no fue significativamente distinta entre los pacientes al considerar su ECOG basal (log rank = 0,593, p = 0,743), las líneas previas de quimioterapia recibida (log rank = 2,117, p = 0,548), el IMC basal (log rank = 2,686, p = 0,261), o el tipo de tumor (log rank = 2,066, p = 0,356). La supervivencia en los pacientes en que fue posible el alta hospitalaria con nutrición parenteral fue superior (log rank = 7,090, p = 0,008). La supervivencia en los pacientes en que se inició la quimioterapia durante o tras iniciar la nutrición parenteral fue también superior (log rank = 17,316, p < 0,001). Un total de 3,6% de los pacientes presentaron infección relacionada con el catéter sin afectar la supervivencia (log rank = 0,061, p = 0,804).

**Conclusión:** la nutrición parenteral en los pacientes oncológicos con obstrucción intestinal y carcinomatosis peritoneal es segura y, en aquellos que responden a qui-

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se who respond to chemotherapy, further administration of home parenteral nutrition together with chemotherapy may enhance prolonged survival.

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Key words: *Parenteral nutrition. Intestinal occlusion. Peritoneal carcinomatosis. Peripherally inserted central catheter. Catheter related infection.*

## Introduction

Intestinal occlusion in oncologic patients may present as abdominal pain or colitis, abdominal distension, nausea, vomiting, and no gas or stools. These symptoms vary depending on the level of the obstruction, but in patients with advanced or end-stage digestive or gynecologic cancers, bowel obstruction is usually insidious, evolving over several weeks, and with spontaneous remission between episodes<sup>1</sup>. Malignant bowel obstruction may appear with incurable intra-abdominal cancer or extra-abdominal primary cancer with intraperitoneal spread (notably breast cancer or melanoma), and this complication may occur in 10%-30% of all colorectal cancers and in 20%-50% of all ovarian cancers<sup>2</sup>.

At first presentation, intestinal occlusion secondary to malignancy may be treated with surgery which can produce resolution in many cases, but recurrence can render repeat surgery unsuccessful<sup>3</sup>. At this stage, the focus of treatment for the patient becomes palliation, and survival is likely to be limited (from less than 2 weeks to 2 months) without parenteral support, depending on grade of obstruction and pre-morbid state<sup>4</sup>.

In several countries there has been a trend towards increasing the use of home parenteral nutrition in palliative malignancy, with and without intestinal occlusion<sup>5,6</sup>, but considerable uncertainty exists about indications. Some authors argue that home parenteral nutrition extends survival and facilitates palliative chemoradiotherapy, but others state that the treatment is expensive, and with a high burden to patients during a limited remaining life span<sup>7,8</sup>.

In this study, we aimed to analyze the effects of parenteral nutrition in oncologic patients with intestinal occlusion and peritoneal carcinomatosis regarding prognosis, and the influence of the type of tumor, functional status and other variables that could possibly be associated with survival at our center.

## Materials and Methods

### Patients

All patients attended at the Hospital Universitario Ramón y Cajal at the Oncology ward from 2007 to 2012 with advanced cancer and intestinal occlusion

mioterapia, el uso de la nutrición parenteral domiciliaria, junto con en tratamiento antitumoral activo, aumentan la supervivencia.

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Palabras clave: *Nutrición parenteral. Obstrucción intestinal. Carcinomatosis peritoneal. Catéter central de inserción periférica. Infección relacionada con el catéter.*

with peritoneal carcinomatosis underwent a consultation for parenteral nutrition. If they were considered candidates for active chemotherapy they also started parenteral nutrition and therefore were included in the study. Those patients who were not considered candidates for ongoing chemotherapy were regarded as in need for palliative care and excluded of this study, whether or not receiving parenteral nutrition. The inclusion of a control group with no nutritional support was not considered ethical. At our center, there is a specialized team which includes an Intravenous Therapy Team (ITT) taking care of these patients. The ITT was created at our center at 2006, integrated in the Department of Endocrinology and Nutrition, and was fully operative by the end of that year. At that time, a prospective study was started right after all the protocols were designed and all the personnel was adequately trained in order to give the best care to patients with parenteral nutrition, both at in-hospital and at home, and not only regarding their artificial nutrition but also their venous accesses. Data on those patients with home parenteral nutrition (whether oncologic or not) have been published before<sup>9</sup>. The Ethics Committee of the Hospital Ramon y Cajal approved the study and informed consent was obtained from the participants.

### Outcomes and measures

We aimed to identify the effects of parenteral nutrition in these patients regarding prognosis. Survival from the starting of parenteral nutrition was recorded. Also, if active chemotherapy was started during or after parenteral nutrition was also taken into account when analyzing survival. Active treatment with chemotherapy was started after parenteral nutrition in those patients who presented indication for further lines of chemotherapy as well as a good performance status and no contraindication to continue with chemotherapy, according to the current protocols for each type of tumor. The beneficial effects of parenteral nutrition on hospital discharge and continuation with home parenteral nutrition and ambulatory chemotherapy were also recorded.

The Eastern Cooperative Oncology Group test (ECOG) was used to assess every patient's performance status. Previous lines of chemotherapy were also recorded for every patient. Anthropometric parameters

were measured, body mass index (BMI) calculated, and the percentage of weight loss was also recorded. Estimated daily calorie needs were calculated by the Harris-Benedict equation and multiplied by a factor of 1.2. The Malnutrition Universal Screening Tool (MUST) was used for nutritional screening<sup>10</sup>.

#### *Composition and infusion of parenteral nutrition*

Composition of parenteral nutrition followed current guidelines<sup>11,12</sup>. In brief, we prepared parenteral nutrition at our hospital for individualized formulae, and whenever possible, commercial "Ready To Use" (RTU) bags were also employed. In both cases we aimed at 20-35 kcal/Kg/day, with a proportion of 3-6 g/Kg/day for glucose, 1.0 g/Kg/day for amino-acids and less than 1 g/Kg/day for lipids, with 7-10 g/day of essential fatty acids. Vitamins and trace elements were also added by the hospital pharmacy - for those patients who unable to take these supplements. After hospital discharge, when possible, home parenteral nutrition was infused on an intermittent schedule primarily at nighttime. All patients and, when needed, some of their relatives, were appropriately trained for adequate manipulation of both the central catheter and parenteral nutrition infusion pumps and connections. Patients came to our Clinic for follow-up every 15 days at the beginning of the program, and every 1-2 months thereafter. A complete blood test was performed at that moment as well as a clinical history and examination. Catheter inspection was also done at the ITT clinic at the same time.

#### *Central venous catheters and its related complications*

Choice of CVC was not randomized but based on the patient's responsible physician, always taking into account the underlying disease, the expected duration of HPN, and the possibility of a safe procedure for obtaining a venous access. Ports and Hickman catheters were implanted at the Intervention Radiology Department, with fluoroscopy guidance and local anesthesia. PICCs were implanted at the ITT clinic, with local anesthesia, and with ultrasound guidance. Maximal barrier precautions were maintained for all catheter insertions.

Local catheter infections were defined as an exit site infection (defined as redness, swelling, tenderness, with an erythema of more than twice the diameter of the catheter), tunnel infection, or pocket infection. Catheter-related bloodstream infections (CRBSI) were considered when a patient presented with bacteremia or fungemia in the presence of signs and symptoms of systemic infection, such as fever, chills, and hypotension in the absence of hypovolemia or a cardiac event. A febrile episode in a patient with HPN was regarded as a suspected CRBSI, which was confirmed at our

center with positive semi quantitative or quantitative culture of the catheter after its removal, or positive blood cultures drawn through the catheter and peripheral vein sequentially.

#### *Statistical analysis*

This was a pilot study so no sample size calculation was initially performed for the specific outcomes of this study. Results are expressed as means  $\pm$  SD unless otherwise stated. The Kolmogorov-Smirnov statistic was applied to continuous variables. Logarithmic or square root transformations were applied as needed to ensure a normal distribution of the variables. Comparisons between the different groups at baseline were performed by independent *t* test for continuous variables or the Mann-Whitney U test for non-normal distributed variables, and by  $\chi^2$  test or Fisher's exact test for discontinuous variables. For more than two groups, comparisons were performed by using univariate analysis of variance for continuous variables or Kruskal-Wallis test for non-normal distributed variables, and using the  $\chi^2$  test for discontinuous variables, as needed. Survival was analyzed by Kaplan-Meier estimator, the log rank test and multivariate Cox proportional hazards test. Analyses were performed using SPSS 15 (SPSS Inc, Chicago, Illinois). *P* < 0.05 was considered statistically significant.

#### **Results**

Fifty five patients were included in the study. Age was 60 $\pm$ 13y, baseline ECOG 1.5  $\pm$  0.5 points and BMI 21.6 $\pm$ 4.3 Kg/m<sup>2</sup>. Malnutrition was present in 85% of the included patients. Of all patients, 38 (69.1%) had gastrointestinal tumors, 10 (18.2%) had gynecological tumors and the rest 7 (12.7%) other types which produced intestinal occlusion (urinary tract, unknown origin, pelvic sarcomas). Baseline characteristics of the patients classified according to tumor type are shown in table I. Patients in the group of gastrointestinal tumors and gynecological tumors had lower ECOG scores than patients in the other group, and patients in the group of gynecological tumors had parenteral nutrition for longer time (Tabla I).

Median survival from the start of parenteral nutrition in the whole group of patients was 40 days (range 2-702). It was not significant when considering baseline ECOG (log rank = 0.593, *P* = 0.743), previous lines of chemotherapy (log rank = 2.117, *P* = 0.548), baseline BMI (log rank = 2.686, *P* = 0.261), or type of tumor (log rank = 2.066, *P* = 0.356). Survival in patients who received home parenteral nutrition after hospital discharge was higher than those who stayed in-hospital (log rank = 7.090, *P* = 0.008) (Fig. 1). A 51% of patients could further receive chemotherapy after starting parenteral nutrition, due to an improvement in their sta-

tus. Survival in patients who started chemotherapy during or after parenteral nutrition was higher than those who did not so (log rank = 17.316,  $P < 0.001$ ) (Fig. 2). A total of 3.6% of patients presented CRBSI without affecting survival (log rank = 0.061,  $P = 0.804$ ).

Multivariate Cox proportional hazards test was then performed introducing age, BMI, ECOG, previous lines of chemotherapy, the administration or not of ambulatory chemotherapy after starting parenteral nutrition, the administration or not of home parenteral nutrition, and the type of tumor. The model retained BMI ( $B=0.085$ ,  $P = 0.020$ ), home parenteral nutrition ( $B=1.416$ ,  $P = 0.002$ ) and ambulatory chemotherapy after hospital discharge ( $B = 1.832$ ,  $P < 0.001$ ) as the significant factors associated with survival ( $-2\log Ver = 232.836$ ,  $\chi^2 = 28.363$ ,  $P < 0,001$ ).

## Discussion

In this study, we have shown that parenteral nutrition in oncologic patients with intestinal occlusion and peritoneal carcinomatosis might enhance survival when associated with a response to chemotherapy. In fact, those patients achieving a response with subsequent hospital discharge and continuation of treatment with ambulatory chemotherapy and home parenteral nutrition showed higher survival.

Our results are in agreement with a recent study which included 115 women with gynecological cancer with advanced disease<sup>13</sup>, showing that, while burden of disease as assessed on CT scan was not associated with survival, parenteral nutrition associated with concurrent chemotherapy showed a 5 week survival

**Table I**  
Baseline characteristics of patients classified according to type of tumor

|                                       | Gastrointestinal tumors<br>(n=38) | Gynecological tumors<br>(n=10) | Other tumors (n=7) |
|---------------------------------------|-----------------------------------|--------------------------------|--------------------|
| Age (years)                           | 61.71 ± 13.63                     | 51.60 ± 11.73                  | 56.57 ± 11.21      |
| Weight (Kg)                           | 57.81 ± 10.05                     | 55.40 ± 17.45                  | 64.67 ± 16.52      |
| Height (m)                            | 1.64 ± 0.09                       | 1.61 ± 0.07                    | 1.71 ± 0.09        |
| Body mass index (Kg/m <sup>2</sup> )  | 21.63 ± 3.62                      | 21.25 ± 6.40                   | 22.15 ± 5.07       |
| Serum total proteins (g/dL)           | 5.57 ± 0.93                       | 5.50 ± 0.99                    | 5.01 ± 0.92        |
| Lines of chemotherapy (n)             | 1.82 ± 1.04                       | 2.20 ± 1.14                    | 1.43 ± 0.53        |
| ECOG scale (points)                   | 1.53 ± 0.51                       | 1.30 ± 0.48                    | 2.00 ± 0.58†       |
| Time with parenteral nutrition (days) | 54.13 ± 114.99                    | 60.70 ± 44.49*                 | 34.29 ± 57.53†     |

Data are means ± SD. \* $P < 0.05$  vs. group with gastrointestinal tumors, † $P < 0.05$  vs. group with gynecological tumors.

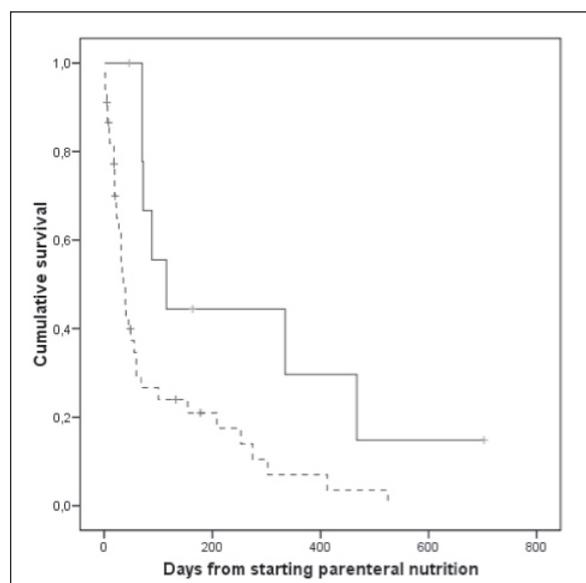


Fig. 1.—Survival in patients who received home parenteral nutrition after hospital discharge (black line) vs those who stayed in-hospital (dashed line).

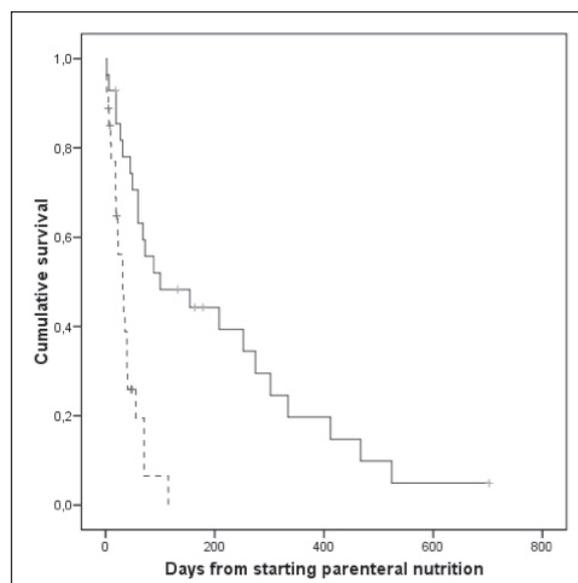


Fig. 2.—Survival in patients who started chemotherapy during or after parenteral nutrition (black line) vs those who did not so (dashed line).

benefit<sup>13</sup>. Another recent study, involving a large prospective multinational case series of 414 patients with advanced cancer –approximately 67% with intestinal occlusion– treated with parenteral nutrition during palliative malignancy, showed a median survival of 91 days, a 50% mortality at 3 months, and a 77% mortality at 6 months<sup>4</sup>. On the other hand, older studies such as one from Abu-Rustum and colleagues in 1997, showed only a 17 day survival advantage with parenteral nutrition in ovarian cancer patients receiving chemotherapy, and they concluded that the short survival benefit did not justify the use of parenteral nutrition<sup>14</sup>. It is possible that the improvement in anticancer therapies over the years contributes substantially to the enhanced survival seen in recent studies.

A recent meta-analysis including twelve studies involving 437 patients on parenteral nutrition with palliative malignancy and inoperable bowel obstruction, revealed a mean survival of 116 days, median 83 days, with 45% and 24% still alive at 3 and 6 months, but only 2% survival at one year<sup>8</sup>. The health economic analysis demonstrated high associated costs in this meta-analysis and the authors concluded that decisions about starting parenteral nutrition in patients with palliative malignancy are difficult, and that such decisions vary according to country, clinician attitudes, and local economies<sup>8</sup>. Therefore, it is of utmost interest to report results from local experience, such as our study, which may guide decision making.

The clinical challenge is to accurately identify those patients who are likely to survive for long enough to benefit from parenteral nutrition treatment. The recommendation in the European 2009 guideline that parenteral nutrition may be considered if the anticipated survival is longer than 2-3 months<sup>12</sup>, is predominantly based on quality of life data showing that quality of life parameters were considered to remain largely stable until 2-3 months before death<sup>5,15</sup>. Besides, although it has been suggested that Karnofsky performance score and type of malignancy can statistically discriminate between longer and shorter survival, there is substantial overlap between the categories<sup>8</sup>.

In our study, we analyzed several variables that could have been associated with survival, such as the type of tumor, the presence of malnutrition at baseline, the lines of previous received chemotherapy, age, and ECOG score. We found that none of these variables could predict survival although we selected candidates for PN with relatively good ECOG scores, possible precluding any association between functional status with survival. The aforementioned study by Bozzetti and colleagues<sup>4</sup> suggested the potential predictive value of combining Glasgow Predictive Score and Karnofsky performance score to identify the probability of surviving up to 3 and 6 months, but this requires further investigation.

Some issues regarding safety of parenteral nutrition need also to be discussed: the risk of central ca-

theter-related infections, the thrombotic and metabolic complications, and the possibility of parenteral nutrition-induced tumor growth. The latter has been recently reviewed by Bossola and colleagues, who reported conflicting and inconclusive evidence<sup>16</sup>.

Regarding central catheter-related infections, the meta-analysis from Naghibi and colleagues [8] showed central venous catheter sepsis rates which ranged from 0.40 to 2.89 per 1000 days. A recent multicenter study has explored the complications of home parenteral nutrition concluding that line infections were the most important one<sup>17</sup>. They found an incidence of 3.6 per 1000 catheter-days, and this number increased when considering patients with a multi-use central venous catheter to 11.6 per 1000 catheter-days. We have reported a low rate of catheter-related infections, especially with the use of peripherally inserted central catheters<sup>9,18</sup>. In the present study, the rate of catheter related infection was low and it has no influence on survival, therefore parenteral nutrition support in these patients can be considered relatively safe when appropriately managed by an experienced team, as it occurs at our center.

Thrombotic complications were reported before in patients with malignancy and parenteral nutrition, with a wide discrepancy between them, showing rates from 0.19 per 1000 days<sup>14</sup> and 4.34 per 1000 days (although 5 out of the total of 6 thrombotic episodes in the latter study were in the same patient)<sup>19</sup>. Metabolic complications were also reported to be low ranging from 0.32 to 1.37 per 1000 days<sup>20-22</sup>. In our study, we have not found any thrombotic episodes or any severe metabolic complications.

In conclusion, our data show that parenteral nutrition in patients with advanced cancer and intestinal occlusion is safe, and in those who respond to chemotherapy, further administration of home parenteral nutrition may enhance prolonged survival.

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