Annals of Oncology 25: 487–493, 2014
doi:10.1093/annonc/mdt549
Published online 9 January 2014

The prognosis of incurable cachectic cancer patients on home parenteral nutrition: a multi-centre observational study with prospective follow-up of 414 patients

F. Bozzetti[1], L. Santarpia[2], L. Pironi[3], P. Thul[4], S. Klek[5], C. Gavazzi[6], M. Tinivella[7], F. Joly[8], C. Jonkers[9], J. Baxter[10], L. Gramlich[11], L. Chicharro[12], M. Staun[13], A. Van Gossum[14], S. Lo Vullo[15] & L. Mariani[15]*

[1]Faculty of Medicine, University of Milan, Milan; [2]Clinical Nutrition and Internal Medicine, Department of Clinical and Experimental Medicine, Federico II University, Naples; [3]Department of Gastroenterology and Internal Medicine, St. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy; [4]Department of General, Visceral, Vascular and Thoracic Surgery, Charité Campus Mitte, Humboldt-University, Berlin, Germany; [5]General Surgery Unit, Stanley Dudrick Memorial Hospital, Skawina, Poland; [6]Unit of Nutritional Support, Fondazione IRCCS Istituto Nazionale Tumori, Milan; [7]SSD Dietetica e Nutrizione Clinica, A.O.U. San Luigi Gonzaga, Orbassano, Italy; [8]Department of Gastroenterology and Nutrition Support, Beaujon Hospital, René Diderot University of Paris, Paris, France; [9]Department of Dietetics, Academic Medical Center, Amsterdam, The Netherlands; [10]Centre for Managed Clinical Networks, Kings Cross Community Care Centre, Dundee, UK; [11]Nutrition Support, Division of Gastroenterology, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada; [12]Unidad de Soporte Nutricional, Hospital Vall d'Hebron, Barcelona, Spain; [13]Department of Gastroenterology CA-2121, Rigshospitalet, Copenhagen, Denmark; [14]Clinic of Intestinal Diseases and Nutritional Support, Department of Gastroenterology, Erasme Hospital (Université Libre de Bruxelles), Brussels, Belgium; [15]Unit of Clinical Epidemiology and Trial Organization, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy

Received 3 October 2012; revised 22 March 2013and 19 July and 20 November 2013; accepted 20 November 2013

Background: The role of home parenteral nutrition (HPN) in incurable cachectic cancer patients unable to eat is extremely controversial. The aim of this study is to analyse which factors can influence the outcome.

Patients and methods: We studied prospectively 414 incurable cachectic (sub)obstructed cancer patients receiving HPN and analysed the association between patient or clinical characteristics and surviving status.

Results: Median weight loss, versus pre-disease and last 6-month period, was 24% and 16%, respectively. Median body mass index was 19.5, median KPS was 60, median life expectancy was 3 months. Mean/median survival was 4.7/3.0 months; 50.0% and 22.9% of patients survived 3 and 6 months, respectively. At the multivariable analysis, the variables significantly associated with 3- and 6-month survival were Glasgow Prognostic Score (GPS) and KPS, and GPS, KPS and tumour spread, respectively. By the aggregation of the significant variables, it was possible to dissect several classes of patients with different survival probabilities.

Conclusions: The outcome of cachectic incurable cancer patients on HPN is not homogeneous. It is possible to identify groups of patients with a ≥6-month survival (possibly longer than that allowed in starvation). The indications for HPN can be modulated on these clinical/biochemical indices.

Key words: cancer cachexia, home parenteral nutrition, incurable cancer patient, malignant obstruction

introduction

The indication for home parenteral nutrition (HPN) in incurable patients who are unable to eat, mainly for malignant obstruction, is extremely controversial and its use in Europe is considerably different from one country to another, accounting for 60% of all patients' population on HPN in the Netherlands and Italy to only 5% in the UK, while the remaining European countries are in between [1].

This is not unexpected because a variety of cultural factors, traditions, religious beliefs, local preferences, as well as a multitude of other social and economic factors influence decision making in nutrition for both healthy and ill people [2].

Some authors, following a simple logic of cost/effectiveness ratio, do not recommend HPN because, while most of patients with benign intestinal failure can survive many years 'thanks' to HPN, most of patients with malignant obstruction die within weeks or months 'despite' HPN. On the contrary, others argue that some of these cancer patients actually die 'with' the tumour but not 'because' of the tumour, but because of starvation. In fact, some selected studies of incurable cancer patients receiving HPN because of malignant (sub)obstruction report a median

*Correspondence to: Dr Luigi Mariani, Unit of Clinical Epidemiology and Trial Organization, Fondazione IRCCS Istituto Nazionale Tumori, Via G. Venezian 1, 20133 Milan, Italy. Tel: +39-02-2390-3199; Fax: +39-02-2390-2095; E-mail: luigi.mariani@istitutotumori.mi.it

survival of 5–6 months or more, which is longer than the usual survival time after total macronutrient deprivation (~2–2.5 months for healthy people) (references in [3]). These patients, if not nutritionally supported, would obviously die due to undernutrition rather than to tumour progression.

Few studies (and none prospectively) have reported that Karnofsky Performance Status (KPS), level of serum albumin and of serum cholinesterase are prognostically significant (references in [3]); however, these scattered data proved unsuitable to guide the clinician in the recommendation of HPN. As a consequence, the European [4] and American [5] guidelines on HPN are also quite vague on this issue.

Rather than assuming a dogmatic position when facing this dilemma, we felt that a prospective investigation aimed to define if some patient- or tumour- related characteristics are associated with survival length, would be worthwhile.

patients and methods

study design and patients

The idea of investigating which factors may be significantly associated with the survival of incurable cancer patients receiving HPN was originally conceived within the Home Artificial Nutrition Working Group (HANWG) of the European Society for Clinical Nutrition and Metabolism. A prospective protocol was approved by the members of the HANWG and distributed to Centres potentially involved in HPN programmes in cancer patients. On each patient's discharge, participating centres were asked to fill up an *ad hoc* form including the following data: demographic, nutritional [usual and current body weight, body mass index (BMI)], clinical–oncological (life expectancy, KPS, site of primary, histopathology, tumour spread and vital organ involvement, previous oncologic treatments), biochemical variables [blood cell count, serum albumin, C-reactive protein (CRP)], indications for HPN, start date, end date and method of HPN administration and management and date of death. Furthermore, centres were required to provide additional information concerning major complications, HPN withdrawal and likely cause of death (HPN-related, organ failure or progressive wasting). For all surviving patients, it was required a minimum period of observation of at least 6 months. Body weight loss and the Glasgow Prognostic Score (GPS) were then calculated.

Centres recommended HPN according to individual institutional policies without any interference by HANWG responsible for the protocol, in compliance with the purposes of an observational study.

The patient admission criteria were the following: adults/elderly patients with no or negligible oral/enteral nutrition (usually because of intestinal obstruction/sub-obstruction, diagnosed on clinical/radiological ground and refractory to previous medical care), presence of an incurable malignancy, without major organ failure or major involvement of a vital organ or severe metabolic derangement. In addition, patients with ascites or pleural effusion (which might be exacerbated by the fluid infusion) and those with uncontrolled symptoms or those receiving HPN in the perspective to become candidate to a future oncologic treatment were excluded. It was required the prescription of an i.v. nutritional daily regimen including at least 25 kcal and 1 g amino acid/kg bodyweight. Each centre was granted permission to take part to the study from its own local Human Investigations Committee.

statistical analysis

Descriptive analyses were based on standard statistics such as relative frequencies for categorical variables (gender, age class, tumour site, tumour spread, main extent of disease, vital organ involvement, most recent therapy, GPS) or with medians and ranges for continuous variables (age, relative weight loss, BMI, CRP, serum albumin, KPS). Relative weight loss was computed either with reference to the usual weight, or with respect to the weight measured 6 months before HPN start; the latter value was also treated as categorical towards a 10% classification cut-off.

The study end point was overall survival (OS), calculated from the date of HPN start to the date of death for any cause, with censoring at the date of last follow-up assessment in alive subjects. The minimum follow-up duration for the latter was 6 months. Survival data were summarized by computing the OS curve with the Kaplan–Meier method. However, for the sake of simplicity, statistical analyses were carried out considering survival status at 3 or 6 months as a dichotomous variable.

In order to investigate the association between distinct patient or clinical characteristics and 3- or 6-month survival, Pearson's χ^2 tests were used for univariable analyses, while logistic regression models were used for multivariable analyses.

Two-sided P values below the conventional 5% threshold were considered statistically significant. Statistical analyses were carried out with the SAS package (Version 9.2, SAS Institute, Cary, NC) and R software (R Foundation for Statistical Computing, Vienna, Austria).

results

study population

Thirteen centres from 10 different countries collected information for 419 consecutive, incurable cancer patients receiving HPN during a 6-year period (between November 2004 and March 2011). Five patients were not considered for the following reasons: HPN as a part of an already planned subsequent oncologic therapy (two cases); impossible diagnostic differentiation between incurable disease and radiation enteropathy (one case); missing follow-up information (two cases). Consequently, the investigated sample included 414 patients.

Series characteristics are summarized in Table 1. Noteworthy, patients were severely malnourished, as reflected by a median weight loss, 24% of the usual weight and 16% of the weight measured 6 months before entering into the study and a median BMI of 19.5. Median KPS was 60, median life expectancy was 3 months, more than half patients had a primary abdominal gastrointestinal tumour, (sub)obstruction occurred as indication for HPN in approximately two thirds of the cases.

Patients' age was 65 years or older in 41% of the cases, and 92% of the patients were classified as stage IV according to the SCRINIO classification of cancer cachexia [6].

The i.v. nutritional support was continued till patient's death in the majority of cases, and withdrawn earlier in one third of them ($n = 139$, 33.6%) for the following reasons: pre-agonic status ($n = 101$, 24.4%), patient/relatives refusal ($n = 29$, 7.0%); onset of HPN-catheter-related complications ($n = 9$, 2.2%). For these 139 patients, median survival time after HPN discontinuation was 2 months (range 1–126 months) overall. Median survival time was longer in the subsets of patients who discontinued HPN because of patient/relatives refusal (5 months, range 1–61) or HPN-catheter related complications (6 months, range 3–49).

survival analysis

At study conclusion, all patients except 12 (2.9%) were dead. Median survival, 3.0 months (95% confidence interval 2.7–3.3 months) in the overall series (Figure 1), showed little between-

Table 1. Main patient and disease characteristics

	N	%
Overall	414	–
Gender		
Female	190	45.9
Male	224	54.1
Age, years		
Up to 64	244	58.9
65 or higher	170	41.1
Median (range)	62 (16–90)	
Relative weight loss, % (83 missing)		
Median (range)	24 (−8[a]–56)	
Relative weight loss in the last 6 months, % (84 missing)		
Median (range)	16 (−44[b]–50)	
BMI, kg/m^2 (2 missing)		
Overall: median (range)	19.5 (12.8–30.0)	
Age <65 years: median (range)	19.5 (12.9–30.0)	
Age ≥65 years: median (range)	19.6 (12.8–27.7)	
Karnofsky Performance Status (26 missing)		
Median (range)	60 (20–100)	
Life expectancy, months (8 missing)		
Median (range)	3 (0–24)	
CRP, mg/l (43 missing)		
Median (range)	8.0 (0.0–321.0)	
Serum albumin, g/100 ml (19 missing)		
Median (range)	3.2 (1.8–5.0)	
Glasgow Prognostic Score		
0	60	16.6
1	172	47.5
2	130	35.9
N.A.	2	–
Overall	414	–
Tumour site		
Head and neck	50	12.1
Stomach	92	22.2
Small bowel–biliary	10	2.4
Colon–rectum	84	20.3
Ovary	51	12.3
Pancreas	46	11.1
Other	81	19.6
Histological type		
Carcinoma	378	91.75
Sarcoma	13	3.16
Melanoma	6	1.46
Mesothelioma	4	0.97
Glioblastoma	3	0.73
Pseudomixoma	3	0.73
Lymphoma	2	0.49
Neuroendocrine	2	0.49
N.A.	2	–
Tumour spread		
Locoregional	131	32.2
Metastatic	105	25.8
Both	171	42.0
N.A.	8	–
Main extent of disease		
Extra-abdominal	60	16.1
Intra-abdominal	269	72.3
Both	43	11.6
N.A.	42	–
Vital organ involved		
No	137	41.4
Yes	194	58.6
N.A.	83	–
Most recent therapy		
Surgery	53	16.9
RT	24	7.6
CT 1st line	89	28.3
CT 2nd line	71	22.6
CT 3rd line	77	24.5
N.A.	100	–

BMI, body mass index; N.A., not available; CRP, C-reactive protein.
[a]One patient showed increased weight, two stable weight.
[b]Six patients showed increased weight, two stable weight.

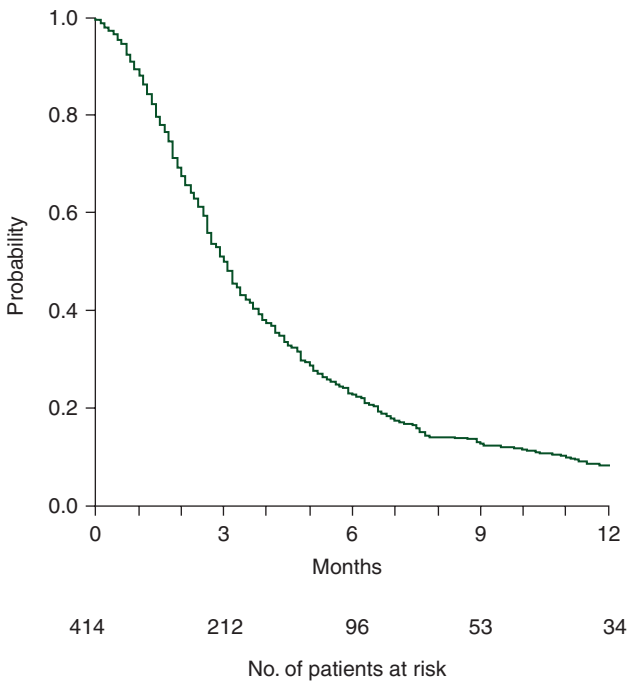

Figure 1. Overall survival curve of the entire series.

centre variability (from 1.3 to 4.5, with widely overlapping confidence limits, when estimable).

At 3 and 6 months after HPN start, 50.0% and 22.9% patients were alive, respectively. The 3- and 6-month survival estimates were 56.9% and 27.7%, respectively, for patients without metastatic involvement of vital organs at the start of HPN, and 44.9% and 16.4%, respectively, for those with vital organ involvement.

With reference to the 143 patients (approximately one-third of the series) with the so-called refractory cachexia [7], 3- and 6-month survival dropped to 29.4% and 8.4%. These figures were 31.7% and 12.2% for patients without vital organ involvement, 27.1% and 5.9% for those with vital organ involvement.

Table 2. Cause of death distribution in the whole series and according to vital organs involvement[a]

	N	%
Whole series	402	
HPN/CVC complications	5	1.2
Vital organ failure	185	46.0
Progressive wasting	136	33.8
Unknown	76	18.9
Vital organs not involved	133	
HPN/CVC complications	2	1.5
Vital organ failure	31	23.3
Progressive wasting	88	66.2
Unknown	12	9.0
Vital organs involved	190	
HPN/CVC complications	3	1.6
Vital organ failure	131	68.9
Progressive wasting	24	12.6
Unknown	32	16.8

CVC, central venous catheter.

[a]The number of deaths in patients with or without organs involved does not add up to the total number of deaths because of the exclusion of 79 dead patients with missing information on organ involvement.

Cause of death, either overall or according to the presence/absence of vital organ involvement at HPN start, is shown in Table 2.

association between main factors and surviving status

Number and percentage of surviving patients and *P* values at the univariable analyses are reported in Table 3. Significant results were obtained for tumour spread, vital organ involvement, KPS and GPS on both end points, and for relative weight loss on 6-month survival only. However, in the multivariable analyses (Table 4), a significant and independent prognostic effect was confirmed for KPS and GPS on 3- and 6-month survival, and for tumour spread on 6-month survival. Survival probability figures estimated for the combination of the above factors are shown in Table 5. One may observe the substantial variability of survival figures. In particular, 3-month survival ranged from a minimum of 33% for patients with KPS ≤ 50 and GPS = 2 to a maximum of 79% for patients with KPS > 50 and GPS = 0. As regards to 6-month survival, a minimum of 6% was estimated for patients with KPS ≤ 50, GPS = 2 and extensive tumour spread, while a maximum of 61% was estimated for patients with KPS > 50, GPS = 0 and locoregional tumour spread.

discussion

This study involved 414 cachectic patients with an incurable malignancy receiving HPN, mainly for intestinal (sub)obstruction and without a concurrent oncologic therapy. Median relative weight loss was 24% and 92% of them had a weight loss $\geq 10\%$ which means that almost all could be defined as cachectic according to two validated cancer cachexia classifications published in literature [6, 8].

We observed a mean/median survival of 4.7/3.0 months, a finding quite similar (or a bit lower) to that of many retrospective and prospective series and in agreement with the common expectation in advanced cancer patients belonging to an area of simple palliation (references in [3]).

The statistically significant prognostic variables were KPS, tumour spread (categorized as local-locoregional, metastatic or both) and GPS. Except for KPS, which was already reported in literature, tumour spread and GPS were never investigated before. All these indexes are simple, commonly reported in the oncologic charts, objective and can be easily quantified.

In absence of a proper control group, we cannot definitely assess which was the clinical impact of HPN. However, from a careful scrutiny of the literature (references in [3]), we found that the survival of patients with malignant obstruction usually does not exceed 2 months if no PN support is supplied during the hospital stay and is further reduced to <2–3 weeks if patients are followed at home.

In contrast, our data showed that about 50% of the patients on HPN survived longer than what is usually observed in historical controls, and approximately one-quarter survived 6 months or longer—median survival beyond 6 months being 4.1 months. Hence, it might be that these patients benefitted from HPN in terms of longer survival. We are aware that no hard data are supporting this statement; however, parenteral nutrition of (hypo)aphagic patients is somewhat viewed as a life-saving procedure because some incurable cancer patients can survive several months [9] but the onset of aphagia drastically reduces the survival time to few weeks. In addition, a RCT to definitely set the issue would be considered unethical by many nutritionists and, on the contrary, an over-treatment by some clinicians who fear PN might only prolong and worsen symptoms of the patients.

With reference to 3-month survival, we observe that, combining information on the GPS and the KPS, distinct patients populations at higher or lower chance of survival may be discriminated (Table 5). Similarly, the combinations of the KPS, the GPS and the pattern of tumour spread leads to 18 distinct patient groups, whose survival at 6 months ranges from only 5% to a clinically relevant 43.7% (Table 5).

In summary, depending on the aggregation of different prognostic variables, it turns out that apparently homogeneous incurable weight-losing patients may in fact be prognostically stratified. This could help clinicians to determine HPN indication in the individual patient.

Another pivotal component of patient outcome is the quality of life. A survey [10] on the relevance of quality of life for patients with advanced cancer showed that only 22% of them would choose palliative chemotherapy, in preference to supportive care alone, to benefit from the associated 3-month additional survival advantage, in contrast, 68% would choose chemotherapy if it substantially reduced adverse symptoms without prolonging life. Since an *ad hoc* study [11] has shown that quality of life starts to decline in the last 2–3 months of life of these patients on HPN, this also would argue against recommending HPN in patients with a prognosis of $\leq$3 months.

Table 3. Number (*N*) and percentage (%) of surviving patients at 3 and 6 months

	3 months			6 months		
Category (reference)	*N*	%	*P*	*N*	%	*P*
Gender						
Female	92	48.4	0.554	44	23.2	0.925
Male	115	51.3		51	22.8	
Age, years						
Up to 64	122	50.0	1.000	57	23.4	0.810
65 or higher	85	50.0		38	22.4	
Relative weight loss (83 missing)						
<20	54	46.2	0.469	35	29.9	0.013
20–30	58	50.4		16	13.9	
≥30	54	54.6		22	22.2	
Relative weight loss in the last 6 months (84 missing)						
<13	53	50.0	0.920	29	27.4	0.235
13–20	55	49.1		20	17.9	
≥20	58	51.8		24	21.4	
BMI (2 missing)						
≤18.5	79	51.3	0.741	29	18.8	0.116
>18.5	128	49.6		66	25.6	
Karnofsky Performance Status (26 missing)						
Up to 50	72	37.5	<0.001	19	9.9	<0.001
>50	118	60.2		66	33.7	
Glasgow Prognostic Score (52 missing)						
0	43	71.7	0.001	23	38.3	0.001
1	83	48.3		38	22.1	
2	57	43.8		19	14.6	
Tumour site			0.285			0.448
Head and neck	28	56.0		13	26.0	
Stomach	53	57.6		17	18.5	
Small bowel–biliary	5	50.0		2	20.0	
Colon–rectum	44	52.4		26	31.0	
Ovary	25	49.0		13	25.5	
Pancreas	20	43.5		9	19.6	
Other	32	39.5		15	18.5	
Tumour spread (7 missing)			0.008			<0.001
Locoregional	80	61.1		47	35.9	
Metastatic	51	48.6		19	18.1	
Both	74	43.3		27	15.8	
Main extent of disease (42 missing)			0.190			0.448
Extra-abdominal	31	51.7		11	18.3	
Intra-abdominal	140	52.0		63	23.4	
Both	16	37.2		7	16.3	
Vital organ involvement (83 missing)			0.030			0.014
No	78	56.9		38	27.7	
Yes	87	44.8		32	16.5	

It is noteworthy that about one-third of the patients of this series would have been considered as belonging to the 'refractory cachexia' stage by Fearon et al. [7], yet the mean/median survival of this group was 2.8/2.1 months (3.0/2.6 months in patients without metastatic involvement of vital organs) that means that a small percentage of them could have benefitted from HPN. This argues against the recommendations of these authors who would deny HPN to all these patients and calls for the need of revising current cancer cachexia classifications.

This study has some limitations: since patients died at home, we cannot be sure about the causes of death even if the protocol specified the classification criteria. Moreover, we lack enough information about the possible weaning from HPN in the last days before death and about the exact composition of the nutritional bags and whether these complied with ESPEN recommendations [4] which suggest a relatively high fat to carbohydrate ratio and a high protein load.

In conclusion, our data show that there is a substantial variability in the survival of incurable cachectic patients on HPN, and that such variability is partly explained on the basis of few and simple prognostic factors which may be taken into account

Table 4. Results from the logistic multiple regression model used to investigate the factors associated with 3- and 6-month survival: odds ratio (OR), 95% confidence interval (CI) and *P* value

	3 months		6 months	
Category (reference)	OR (95% CI)	*P*	OR (95% CI)	*P*
Age, years				
IQ range: 54–69	1.12 (0.85–0.47)	0.430	1.00 (0.71–1.39)	0.978
Gender				
Female (male)	0.90 (0.56–1.43)	0.652	0.86 (0.48–1.52)	0.602
Relative weight loss 10%				
Yes (no)	1.04 (0.57–1.88)	0.724	0.94 (0.46–1.92)	0.899
N.A. (no)	0.76 (0.33–1.78)		0.79 (0.29–2.16)	
Tumour site				
Biliary–pancreas (upper GI)	0.52 (0.26–1.06)	0.180	0.78 (0.32–1.94)	0.113
Colon–rectum (upper GI)	0.91 (0.50–1.68)		2.24 (1.06–4.70)	
Ovary (upper GI)	0.86 (0.39–1.90)		1.52 (0.57–4.04)	
Other (upper GI)	0.53 (0.28–0.99)		0.85 (0.39–1.89)	
Tumour spread				
Metastatic (locoregional)	0.55 (0.29–1.03)	0.113	0.39 (0.19–0.83)	0.018
Locoreg. and Metast. (locoregional)	0.57 (0.32–1.03)		0.39 (0.19–0.81)	
Main extent of disease				
Extra-abdominal (intra-abdominal)	0.76 (0.36–1.58)	0.637	0.54 (0.22–1.37)	0.294
Extra- and intra-abd. (intra-abdominal)	0.62 (0.29–1.34)		0.94 (0.34–2.60)	
N.A. (intra-abdominal)	0.88 (0.35–2.19)		1.59 (0.56–4.53)	
Vital organ involvement				
Yes (no)	0.91 (0.52–1.59)	0.272	0.84 (0.41–1.71)	0.857
N.A. (no)	0.58 (0.30–1.13)		0.85 (0.40–1.78)	
Glasgow Prognostic Score				
1 (0)	0.30 (0.15–0.61)	0.006	0.39 (0.18–0.84)	0.016
2 (0)	0.29 (0.14–0.61)		0.25 (0.11–0.61)	
N.A. (0)	0.32 (0.13–0.75)		0.60 (0.23–1.60)	
Karnofsky Performance Status				
Up to 50 (>50)	0.38 (0.25–0.60)	<0.001	0.24 (0.13–0.43)	<0.001

IQ, interquartile; N.A., not available; GI, gastrointestinal.

Table 5. Estimated 3-month and 6-month survival probability

Karnofsky Performance Status	Glasgow Prognostic Score	3-month probability	6-month probability		
			Tumour spread		
			Locoregional	Metastatic	Both
Up to 50	0	0.599	0.274	0.155	0.139
	1	0.356	0.156	0.083	0.074
	2	0.333	0.109	0.056	0.050
>50	0	0.790	0.613	0.435	0.404
	1	0.583	0.437	0.274	0.250
	2	0.558	0.338	0.199	0.180

for assessing HPN indication. While in patients with the best (or the worst) prognostic scores, it is likely easy to reach an agreement on the indication to start (or not to start) a programme of HPN, the recommendation is more controversial in intermediate conditions.

In such cases, we state as important that health professionals, recognizing that feeding is a fundamental element in human relationships and culture, approach these decisions with a special sensitivity for concerns about starvation and abandonment and families' desire to provide love and care.

disclosure

The authors have declared no conflicts of interest.

references

1. ESPEN-Home Artificial Nutrition Working Group. Van Gossum A, Bakker H, Bozzetti F et al. Home parenteral nutrition in adults: a European multicentre survey in 1997. Clin Nutr 1999; 18(3): 135–140.
2. Raijmakers NJ, van Zuylen L, Costantini M et al. Artificial nutrition and hydration in the last week of life in cancer patients. A systematic literature review of practices and effects. Ann Oncol 2011; 22(7): 1478–1486.
3. Bozzetti F. Nutritional support of the oncology patient. Crit Rev Oncol Hematol 2013; 87(2): 172–200.
4. Bozzetti F, Arends J, Lundholm K et al. ESPEN Guidelines on Parenteral Nutrition: non-surgical oncology. Clin Nutr 2009; 28(4): 445–454.
5. August DA, Huhmann MB. American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors. A.S.P.E.N. clinical guidelines: nutrition support therapy during adult anticancer treatment and in hematopoietic cell transplantation. JPEN J Parenter Enteral Nutr 2009; 33(5): 472–500.
6. Bozzetti F, Mariani L. Defining and classifying cancer cachexia: a proposal by the SCRINIO Working Group. JPEN J Parenter Enteral Nutr 2009; 33(4): 361–367.
7. Fearon K, Strasser F, Anker SD et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 2011; 12(5): 489–495.
8. Fearon KC, Voss AC, Hustead DS. Cancer Cachexia Study Group. Definition of cancer cachexia: effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. Am J Clin Nutr 2006; 83(6): 1345–1350.
9. Lunney JR, Lynn J, Foley DJ et al. Patterns of functional decline at the end of life. JAMA 2003; 289(18): 2387–2392.
10. Silvestri G, Pritchard R, Welch HG. Preferences for chemotherapy in patients with advanced non-small cell lung cancer: descriptive study based on scripted interviews. BMJ 1998; 317(7161): 771–775.
11. Bozzetti F, Cozzaglio L, Biganzoli E et al. Quality of life and length of survival in advanced cancer patients on home parenteral nutrition. Clin Nutr 2002; 21(4): 281–288.

Annals of Oncology 25: 493–499, 2014
doi:10.1093/annonc/mdt568

Exercise program improves therapy-related side-effects and quality of life in lymphoma patients undergoing therapy

F. Streckmann[1,2], S. Kneis[1,2], J. A. Leifert[3], F. T. Baumann[5], M. Kleber[1], G. Ihorst[1,4], L. Herich[6], V. Grüssinger[1], A. Gollhofer[2] & H. Bertz[1*]

[1]Department of Hematology and Oncology, Freiburg University Medical Center; [2]Department of Sport Science, University of Freiburg; [3]Comprehensive Cancer Center Freiburg (CCCF), Freiburg University Medical Center; [4]Clinical Trials Unit, Freiburg University Medical Center, Freiburg; [5]Institute of Cardiovascular Research and Sport Medicine, German Sport University, Cologne; [6]Institute of Medical Statistics, Informatics and Epidemiology (IMSIE), University of Cologne, Cologne, Germany

Received 10 September 2013; revised 16 November 2013; accepted 27 November 2013

Background: Lymphoma patients undergoing therapy must cope with the side-effects of the disease itself, therapy and associated immobility. Peripheral neuropathy (PNP), loss of balance control and weakness not only diminishes patients' quality of life (QOL), it can also affect planning and the dosage of therapy. Exercise may enable patients to reverse these declines, improving their performance level and QOL.

Patients and methods: We carried out a randomized, controlled trial, assigning 61 lymphoma patients either to a control group (CG; $N = 31$) or to a 36-week intervention (IG; $N = 30$), consisting of sensorimotor-, endurance- and strength training twice a week. Primary end point was QOL; secondary end points included movement coordination, endurance, strength and therapy-induced side-effects.

Results: Intergroup comparison revealed improved QOL- ($\Delta_{T1–T0}$; $P = 0.03$) and PNP-related deep sensitivity in the IG: 87.5% were able to reduce the symptom, compared with 0% in the CG ($P < 0.001$). Significant differences in the change of balance control could be found between the groups, with the IG improving while the CG steadily declined (monopedal static $\Delta_{T3–T0}$; $P = 0.03$; dynamic $\Delta_{T3–T0}$; $P = 0.007$; perturbed mono-$\Delta_{T3–T0}$; $P = 0.009$ and bipedal $\Delta_{T3–T0}$; $P = 0.006$), failed attempts (monopedal static $\Delta_{T3–T0}$; $P = 0.02$, dynamic $\Delta_{T3–T0}$; $P < 0.001$and perturbed $\Delta_{T3–T0}$; $P = 0.006$) and improved time to regain balance ($\Delta_{T3–T0}$; $P = 0.04$). Moreover, the change in the aerobic performance level ($\Delta_{T3–T0}$; $P = 0.05$) and additional amount of exercise carried out per week [metabolic equivalent (MET); $P = 0.02$] differed significantly across groups.

*Correspondence to: Prof. Hartmut Bertz, Albert Ludwigs University Medical Center, Department of Hematology and Oncology, Hugstetter Str. 55, D-79106 Freiburg, Germany. Tel: +49-761/270-33350; Fax: +49-761/270-32330; E-mail: hartmut.bertz@uniklinik-freiburg.de