Original Article

Non-compliance with end-of-life parenteral nutrition prescription recommendations: retrospective study of 1,260 cancer patients

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Background: Cancer patients near end of life (EOL) often suffer malnourishment and cachexia. In these patients, the prescription of parenteral nutrition (PN) remains highly controversial. Guidelines state that nutritional support does not improve quality of life in dying patients. We aimed to assess the compliance with international recommendations about PN prescription in advanced cancer, identify factors associated with PN at EOL and to evaluate the risk of blood stream infections (BSI).

Methods: Retrospective analysis of data from medical records of patients who died in 2013, 2015, 2017 and 2019 in a cancer center.

Results: One thousand two hundred and sixty patients with advanced cancer were included. PN was prescribed in 574 (45.6%) patients, the mean duration of PN was 10±9.7 days. Patients with a severe malnutrition [odds ratio (OR) =2.36; 95% confidence interval (CI): 1.42–4.02], a malignant bowel obstruction (MBO) (OR =2.25; 95% CI: 1.44–3.56), a length of hospitalization >12 days (OR =2.21; 95% CI: 1.67–2.94), a body mass index (BMI) <22.14 kg/m^2 (OR =2.02; 95% CI: 1.52–2.67), an antitumor treatment (OR =1.58; 95% CI: 1.14–2.20) were more frequently prescribed a PN. BSI was diagnosed in 113 patients (9%) and was more frequent in patients receiving a PN (13% *vs.* 6%; OR =2.01; 95% CI: 1.18–3.54).

Conclusions: International guidelines on PN in EOL cancer patients are poorly applied in the studied settings. Factors associated with the use of PN were low BMI, severe malnutrition, antitumor treatment, increased length of hospitalization. These findings argue for the use of a survival estimation tool and a multidisciplinary integrative care intervention when considering PN.

Keywords: Cancer; parenteral nutrition (PN); blood stream infection (BSI); end-of-life care

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Introduction

Adult cancer patients account for a high percentage, sometimes even the majority, of subjects receiving parenteral nutrition (PN) (1). Patients with advanced cancer and a good prognosis should receive adequate nutritional counselling and support including, if required, PN but only after considering together patients' prognosis and the expected benefit on quality of life, as well as the burden associated with nutritional care (2). Additionally, iatrogenic deterioration of nutritional status should be prevented by adequate prophylactic or symptomatic supportive care comprising "permissive" nutritional support in patients undergoing palliative anti-cancer treatment (2). There remain many controversial issues for and against PN, with proponents emphasizing the social and cultural value of nutrition and patients' fear of starvation, and opponents pointing to very little evidence to support its use due to the lack of demonstrated benefit on quality of life and overall survival in end-of-life patients (3-5). Similarly, PN has not been proven effective in advanced cancer (3) and malignant bowel obstruction (MBO) (6). Moreover, blood stream infections (BSI) are more frequent in patients with advanced cancer and PN (7-9). Overall, there is an agreement that unconditional artificial nutrition in all patients undergoing curative or palliative anticancer therapy is associated with more harm (hyperglycemia, hypertriglyceridemia, refeeding syndrome, oedema, PN-associated liver disease) than benefit, therefore, such practice should not be used (2). For dying patients, European Society of Parenteral and Enteral Nutrition (ESPEN) guidelines outline the ineffectiveness of artificial nutritional support to improve comfort and quality of life, thereby excluding most indications for nutritional support (2). American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) guidelines also state that discontinuation of previously initiated PN near the end of life (EOL) is appropriate (10,11), and ethically permissible as nutritional support cannot reverse weight loss in these patients (11). However, the impact of guidelines has been limited due to the frequently moderate interest of oncologists in nutritional aspects of cancer care (2). This lack of interest still results in an overuse of PN near EOL in cancer patients (12).

This study aims to assess the application of international guidelines by evaluating the use of PN near EOL in patients with advanced cancer. Our secondary objective was to identify factors associated with the use of PN, and the incidence of BSI when using PN in this population. We present the following article in accordance with the STROBE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-499/rc) (13).

Highlight box

What was already known?
- Patients with advanced cancer often suffer cancer-associated cachexia.
- Artificial nutrition is unnecessary at this stage.

What are the new findings?
- Artificial nutrition is overused in patients with advanced cancer.
- PN is associated with high rates of BSI and longer hospital stays.

What is their significance?
- A multidisciplinary integrative care intervention is necessary to discuss the benefit-risk ratio of PN in end-of-life cancer patients.

Methods

Study design and cohort selection

We included all patients who were diagnosed with advanced or metastatic cancer and died during their hospitalization in 2013, 2015, 2017 and 2019.

The inclusion center is a French cancer center caring for more than 5,000 new patients yearly. Data were extracted from our hospital register named Programme de Médicalisation des Systèmes d'Information (PMSI). This register collects healthcare claims for every patient's admission. All data were anonymized. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). At their first consultation, all patients were informed that unless they disagree, their clinical data can be used. The Ethics Committee of our institute (Avignon-Provence Cancer Institute) approved this project as part of our clinical practice self-assessment (first part: chemotherapy in end-of-life cancer patients, second part: PN in end-of-life cancer patients). According to the Jardé decree (November 17th 2016 in France), written informed consent and registration were not required. First, we analyzed only previously and routinely collected information. Individual patient data were documented anonymously. Secondly, patients are informed that anonymized data can be analyzed and collected unless they are opposed.

Main outcome measure and definitions

The main outcome was the use of PN during the hospital stay. Factor associated with the use of PN were analyzed. The rate of BSI when using PN at the EOL of patients with advanced cancer was also evaluated.

PN was defined as an intravenous administration through a central venous access device (port-a-cath or peripherally inserted central catheter), of nutrients using mixtures including at least aminoacids, vitamins electrolytes and minerals (14,15). Parenteral hydration without the above-mentioned elements was not considered as a form of PN. Malnutrition was classified in adult cancer patients and those over 70 years of age as severe or moderate, according to the French guidelines (16).

The incidence of BSI was confirmed by microbiological analyses. Blood samples were drawn in case of clinical signs suggestive of infection. Because of the difficulty to draw at the same time one blood sample from a percutaneous vein and from the catheter tip in EOL cancer patients, we chose to study BSI and not central line associated BSI (17). BSI was defined as the presence of viable bacteria or fungi in the blood (18). PN and BSI were considered in the last hospital stay before the patient's death.

Clinical factors potentially associated with PN use were evaluated. Especially, the diagnosis of MBO was established based on history (metastatic intra-abdominal cancer) and physical examination and was confirmed, when possible, with imaging studies (19).

Data collection

We collected the following data from our computerized hospital systems: (I) demographical patient data as age, sex, length of the hospitalization where death occurred, body mass index (BMI) and Eastern Cooperative Oncology Group performance status (ECOG PS) at onset of hospitalization; (II) previous antitumor treatments, referent physician's specialty (medical or radiation oncology, referent physicians were not specifically trained in nutrition but a dietician was systematically involved in the treatment decisions and could seek help from a nutritionist, and professional experience); (III) follow-up by a palliative care team (PCT); (IV) cancer type: digestive, urinary, respiratory tract, gynecological, head and neck or male cancers, miscellaneous tumors, malignant hemopathy and a separate group of other tumors (sarcoma, melanoma, neuroendocrine tumor and primary central nervous system cancer) for which treatment decisions are discussed in regional specialized multidisciplinary tumor boards; (V) PN, complete/incomplete MBO, and BSI.

Statistical analysis

Descriptive statistics are presented as means [standard deviation (SD)] and medians (ranges) for continuous variables. Discrete variables are reported as counts (percentages). A non-parametric Mann-Whitney test was applied to compare the distribution of continuous variables, and χ^2 test (or Fisher's exact test when appropriate) was used to test the association of categorical variables. Continuous variables were then transformed into categorical variables with the median or a predetermined threshold. Performance status was separated into ECOG PS 0–2 and ECOG PS 3–4.

Potential factors associated with PN were compared on univariate analysis first with χ^2 test or Fisher's exact test when appropriate. A multivariate logistic model based on selected parameters from the univariate analysis (the level of significance was set at a P value of <0.20 for selection) was then performed. In addition, three procedures for selecting variables (forward, backward and stepwise) by minimization of Akaike's information criterion were performed to obtain the most appropriate logistic regression model. Among the variables introduced into the logistic regression model, multiple imputation was performed on variables with missing data (complete/incomplete bowel obstruction and BMI <22.14 kg/m^2), since missing values were less than 5%.

A sensitivity analysis was carried out using a regression model without multiple imputation, which found the same statistically significant variables. A P value of <0.05 was considered to be statistically significant, and all statistical tests were two-sided. Statistical analysis was performed using R software system (version 3.6.1, Vienna, Austria) version 4.0.3.

Results

Patients' characteristics (Figure 1, Table 1)

In 2013, 2015, 2017 and 2019, 1,283 patients died, 1,260 patients were included, and 23 patients were excluded because they had a non-locally advanced or a non-metastatic cancer. There was no change in the rate of PN between 2013 and 2019; 80% of the patients had a poor performance status (ECOG PS >2). The mean BMI was 22.8±4.9 kg/m^2 (median: 22.14 kg/m^2). Most patients (89%) were severely malnourished. The median duration of hospitalization

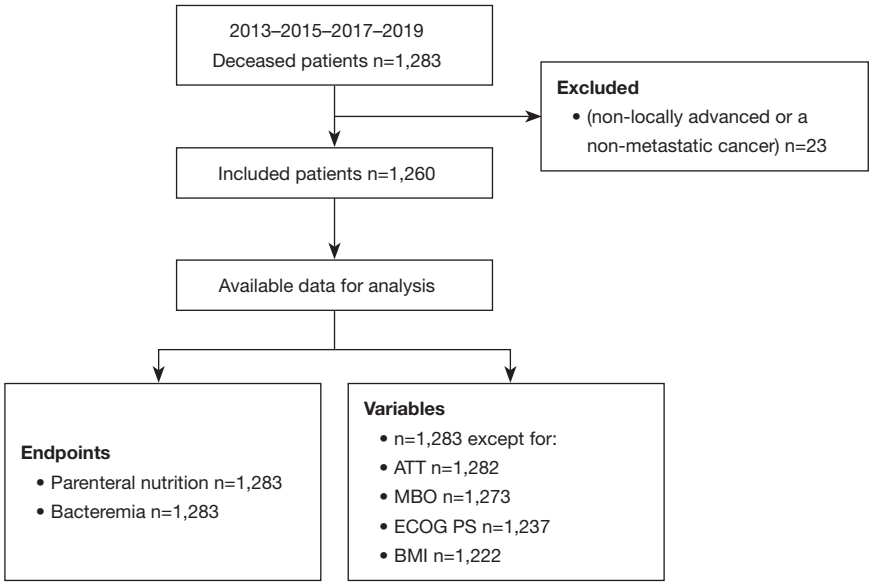

Figure 1 Flow chart. ATT, anti-tumor treatment; MBO, malignant bowel obstruction; ECOG PS, Eastern Cooperative Oncology Group performance status; BMI, body mass index.

Table 1 Patients' characteristics

Variable	Overall (n=1,260)	PN		P value
		No (n=686)	Yes (n=574)	
Age (years)[1]	68 [12]	68 [12]	68 [12]	0.40
Age >69 years[2], n [%]	656 [52]	362 [53]	294 [51]	0.58
Length of stay in days[1]	15 [13]	13 [12]	18 [13]	<0.001
Length of stay >12 days[2], n [%]	655 [52]	293 [43]	362 [63]	<0.001
Physician's experience in years[1]	16 [9]	16 [9]	16 [9]	0.69
Gender, n [%]				0.23
Female	504 [40]	264 [38]	240 [42]	
Male	756 [60]	422 [62]	334 [58]	
BMI's classification, n [%]				<0.001
BMI <22.14 kg/m^2	601 [50]	276 [43]	325 [59]	
Missing data	58	37	21	
Nutritional status, n [%]				<0.001
No malnutrition	19 [2.1]	14 [3.0]	5 [1.1]	
Moderate malnutrition	81 [8.9]	56 [12]	25 [5.6]	
Severe malnutrition	810 [89]	391 [85]	419 [93]	
Missing data	350	225	125	

Table 1 (*continued*)

Table 1 (*continued*)

Variable	Overall (n=1,260)	PN		P value
		No (n=686)	Yes (n=574)	
Physician's specialty, n [%]				0.61
Oncologist	455 [36]	249 [36]	206 [36]	
Radiotherapist	805 [64]	437 [64]	368 [64]	
Cancer's classification, n [%]				
Digestive tract cancer	339 [27]	162 [24]	177 [31]	0.004
Respiratory tract cancer	337 [27]	188 [27]	149 [26]	0.56
Gynecological cancer	204 [16]	115 [17]	89 [16]	0.55
Urinary tract cancer	108 [8.6]	70 [10]	38 [6.6]	0.024
Head and neck cancer	86 [6.8]	44 [6.4]	42 [7.3]	0.53
Male genital cancer	94 [7.5]	60 [8.7]	34 [5.9]	0.11
Rare cancer	59 [4.7]	31 [4.5]	28 [4.9]	0.76
Miscellaneous cancer	20 [1.6]	10 [1.5]	10 [1.7]	0.69
Hematological cancer	13 [1.0]	6 [0.9]	7 [1.2]	0.55
Previous ATT, n [%]				
No ATT	296 [23]	187 [27]	109 [19]	<0.001
ATT within 15 days of death	159 [13]	88 [13]	71 [12]	0.81
New ATT regimen within 30 of death	190 [15]	97 [14]	93 [16]	0.31
Missing data	1	0	1	
PCT follow-up, n [%]	774 [61]	416 [61]	358 [62]	0.057
ECOG PS >2, n [%]	979 [78]	544 [79]	435 [76]	0.088
Complete/incomplete bowel obstruction, n [%]	162 [13]	54 [7.9]	108 [19]	<0.001
BSI, n [%]	113 [9]	41 [6]	72 [13]	<0.001
Length of PN[1]	–	–	10 [9]	–

[1], mean [SD]; [2], median. PN, parenteral nutrition; BMI, body mass index; ATT, anti-tumor treatment; PCT, palliative care team; ECOP PS, Eastern Cooperative Oncology Group performance status; BSI, blood stream infection; SD, standard deviation.

was 15 days (range, 1–80 days). One hundred and sixty-two (13%) patients had a complete/incomplete bowel obstruction. PN was prescribed in 574 (45.6%) patients, mean duration of PN and mean survival from start PN were 10±9.7 and 14.7±11.8 days. BSI was diagnosed in 113 patients (9%).

Factors associated with PN

In univariate analysis (*Table 1*), MBO (19% *vs.* 7.9%), digestive tract cancers (31% *vs.* 24%), a BMI <22.14 kg/m^2 (59% *vs.* 43%), severe malnutrition (93% *vs.* 85%), previous antitumor treatment (81% *vs.* 73%) and a length of hospitalization >12 days (63% *vs.* 43%) were associated with a higher rate of PN at the EOL. The rate of PN was lower among patients with a urinary tract cancer (6.6% *vs.* 10%). In multivariate analysis (*Table 2*), patients with severe malnutrition (OR =2.36; 95% CI: 1.42–4.02), a MBO (OR =2.25; 95% CI: 1.44–3.56), a length of hospitalization >12 days (OR =2.21; 95% CI: 1.67–2.94), a BMI <22.14 kg/m^2 (OR =2.02; 95% CI: 1.52–2.67) were more frequently prescribed a PN whereas patients with a urinary tract cancer received less PN (OR =0.59; 95% CI: 0.39–0.99). The rate of BSI was also higher in patients receiving a PN (13% *vs.*

Table 2 Multivariate analysis

Factors	PN, OR (95% CI)
Severe malnutrition	2.36 (1.42–4.02)
Complete/incomplete bowel obstruction	2.25 (1.44–3.56)
Length of hospitalization >12 days (median)	2.21 (1.67–2.94)
BMI <22.14 kg/m² (median)	2.02 (1.52–2.67)
BSI	2.01 (1.18–3.54)
Antitumor treatment	1.58 (1.14–2.20)
Urinary tract cancer	0.59 (0.35–0.99)

PN, parenteral nutrition; OR, odds ratio; CI, confidence interval; BMI, body mass index; BSI, blood stream infection.

6%), this association remaining statistically significant in multivariate analysis (OR =2.01; 95% CI: 1.18–3.54).

Discussion

Nowadays, around 25,000 patients are estimated to be on home PN in the United States (20). In a retrospective study on patients with advanced cancer, home artificial nutrition was prescribed only to 333 of 29,348 cancer patients (1.1%) (5). Conversely, in the French settings, PN has been found to be much higher and reached up to 13.1% in a study that included 1,301 patients (21). Focusing on EOL cancer patients, the frequency of PN has been estimated to range from 2% to 32% within the last week of life in various countries (12). The higher rates in our study (45.6% of PN near the EOL), are consistent with an overuse of PN in the French settings.

This high figure can easily be explained by the symbolic value of nutrition in cancer patients and ethical, emotional, and cultural aspects heavily influence the decision-making process (22). Indeed, most patients, families, and healthcare professionals believe that increasing food and liquid intake is essential to stave off physical deterioration (22), which is not supported by the available evidence (3). Furthermore, the majority of patients and families express the fear of starvation (22). There is also a strong cultural attachment to food in France. In fact, PN neither improves quality of life nor survival in patients with advanced cancer as demonstrated by two randomized controlled trials. In the first one, 309 cancer patients received erythropoietin and a cyclo-oxygenase inhibitor without (n=170) or with a nutritional support (n=109, about half of patients with PN) (23). No quality-of-life (QoL) assessment was performed but there was no statistically significant difference in survival between intervention and control patients (23). The second trial randomized 70 patients in the PN group and 78 in the oral feeding group (24). The main findings were the lack of improvement in QoL and a negative trend for overall survival among patients treated with PN (median survival 2 *vs.* 3 months) (24). We assume that the French cultural settings might influence the use of PN resulting in the overuse of PN found in the studies on French populations.

In a nationwide study including 32 palliative care units and 1,083 patients, nausea, vomiting, and gastrointestinal obstruction were the most common indications for PN in palliative patients (25). We showed MBO to be another important factor associated with end-of-life PN (OR =2.25; 95% CI: 1.44–3.56). According to the ESPEN guidelines, total inability to eat (malignant bowel failure or complete obstruction) can require timely implementation of artificial nutrition to avoid starvation (2). The position statement of the British Association for Parenteral and Enteral Nutrition (BAPEN) on intestinal failure in patients with malignancy indicates that all patients who may be considered for PN should have an early multidisciplinary team review (nutrition, oncology and PCTs) (26). BAPEN also states that the plans for withdrawal, either at the EOL or any time after commencing, should be discussed (26). The potential benefits of PN in MBO have never been formally established; the Cochrane Library was unable to perform a metanalysis, but data synthesized via a narrative summary did not highlight evidence of the benefit of PN in terms of survival or quality of life (6).

Because of the very low amount of data on this subject, we did not investigate whether the rate of complications was associated with some components of PN. In our study, BMI <22.14 kg/m^2 (OR =2.02; 95% CI: 1.52–2.67) and severe malnutrition (OR =2.36; 95% CI: 1.42–4.02) were found to be independently associated with EOL PN. Malnutrition (low BMI +/– weight loss) (16), or cachexia (weight loss +/– low BMI +/– sarcopenia) (27) occurs in 50–80% of patients with advanced cancer (27,28). The main goal of guidelines is treatment of malnutrition and metabolic derangements in cancer patients (2,10,11). So, ESPEN recommendations leave the possibility of a "permissive" nutritional support in patients with advanced cancer (2). Due to their life expectancy (mean survival of 15 days from the start of hospitalization), most patients we included in our study had a refractory cachexia (27). At this stage of the disease trajectory, cancer patients do not respond to artificial

nutrition aimed at reversing cachexia (27,29). In any case, in hospitalized patients with a normal digestive tract, algorithms of good clinical practice recommend beginning with an oral nutrition support, to try, if unsuccessful, enteral nutrition and to prescribe PN only as a "last resort" (2,30,31). But as PN is an easier and more medical response to nutritional care requests, and as there is an overestimation of cancer patients' survival (32), it is difficult to stop PN (22). We assume that it might contribute to PN sustained at EOL.

Most patients with body weight loss have three or more other uncontrolled symptoms, the most common being early satiety, constipation, nausea or vomiting, mood changes, abnormal taste and smell, abdominal pain (33). Furthermore, cancer patients often experience at EOL a symptom burden that can have an impact on food intake (34). These data advocate for an integrative care intervention and the results of a recent review suggest that a team-based approach, involving palliative care physicians, nurses, dietitians, and occupational therapists, was associated with significant improvement in food intake, nutritional indices, and distress, concurrent with successful management of pain and symptoms (35). Palliative and supportive care teams typically do not yet offer psychosocial interventions for cachexia-related distress. These interventions, tailored to patients' prognosis and cachexia severity, may help patients and family members to cope with cachexia that can render active management of body weight loss no longer possible or appropriate.

Finally, the incidence of BSI was 9%. The rate of BSI has been estimated between 0.27–2.78 episodes/1,000 days in patients with advanced cancer (36). Our results are higher but severe malnutrition and metastatic disease, as seen in end-of-life cancer patients we included, double the risk of developing BSI (37). The other factor to consider is probably the high rate of PN in EOL cancer patients in our study as we highlighted the correlation between PN and BSI (OR =2.01; 95% CI: 1.18–3.54). Total PN administered via central venous catheter has been identified as an independent risk factor of developing BSI in two large studies: (OR =2.65; 95% CI: 2.20–3.19) among 38,674 hospitalized patients with central line, (OR =4.33; 95% CI: 2.50–7.48) in a survey of 4,840 patients in a large tertiary care hospital in New York City who received PN (8,9). A higher incidence of BSI was also demonstrated in cancer patients with PN when compared to those with enteral nutrition [risk ratio (RR) =1.11; 95% CI: 1.04–1.19] in a recent meta-analysis of 43 studies and 2,827 patients (7).

Our study did not allow us to have a precise estimate of BSI. Due to their clinical condition, many patients had incomplete blood samplings. Most clinical records did not provide body weight curve follow-up or PN indications and we did not look at the dose given, which may explain in part the high percentage of PN we noted. We also did not include patients who had died outside of our cancer center, which would have resulted most likely in a decrease of the rate of BSI, because patients with infectious complications are prone to be hospitalized more often. Our study is therefore not representative of PN in all cancer patients at the EOL. Another limit of our study is its retrospective design do not necessarily produce an accurate portrait of care provided to patients who are dying (38).

Conclusions

We showed that PN near the EOL of patients with advanced cancer was overused. MBO, BMI, severe malnutrition and length of hospitalization were correlated with end-of-life PN in cancer patients, and we also demonstrated a higher rate of BSI in patients with PN. These findings argue for the use of a survival estimation tool when considering PN and for a multidisciplinary integrative care intervention in order to discuss and re-assess the benefit-risk ratio of PN in EOL cancer patients.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-499/rc

Data Sharing Statement: Available at https://apm.amegroups.com/article/view/10.21037/apm-22-499/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-499/coif). PD reports personal fees from SANOFI and non-financial support from Bayer Pharma and LVL. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). At their first consultation, all patients were informed that unless they disagree, their clinical data can be used. The Ethics Committee of our institute (Avignon-Provence Cancer Institute) approved this project as part of our clinical practice self-assessment (first part: chemotherapy in end-of-life cancer patients, second part: PN in end-of-life cancer patients).

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