Original Article

Early intervention with supplemental parenteral nutrition reduces the incidence of granulocytopenia-related infections in patients with lung cancer: a retrospective cohort study

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Background and Objectives: The optimal timing for initiating supplemental parenteral nutrition in chemotherapy-induced severe granulocytopenia in patients with lung cancer remains uncertain. **Methods and Study Design:** A retrospective study was conducted among patients with lung cancer from February 2016 to June 2018. In total, 182 eligible patients were included and divided into 2 groups according to the time of supplemental parenteral nutrition intervention: early initiation (within 72 hours of development of granulocytopenia) and late initiation (over 72 hours). The primary outcomes of the study were bacterial infection and fungal infection, and the secondary outcomes were duration of absolute neutrophil count less than 1.0×10^9 cells/L, length of hospital stay, mortality rate, and rate of chemotherapy (4 cycles) completion. **Results:** The incidence rates of bacterial infection and fungal infection were significantly lower among patients who received supplemental parenteral nutrition early than among patients who received it late. No significant difference in mortality was observed between the groups. In addition, compared with late supplemental parenteral nutrition, early supplemental parenteral nutrition was associated with a higher rate of completion of 4 chemotherapy cycles and shorter hospital stays and leukocyte recovery periods in our cohort. Univariate and multivariate logistic regression analyses revealed that the subgroup of patients with an NRS-2002 score of 2 benefited from early supplemental parenteral nutrition. **Conclusions:** Early supplemental parenteral nutrition after chemotherapy-induced severe granulocytopenia could reduce the risk of infection, improve the likelihood of chemotherapy completion, and shorten hospital stays and leukocyte recovery times.

Key Words: myelosuppression, supplemental parenteral nutrition, granulocytopenia, chemotherapy, lung cancer

INTRODUCTION

Chemotherapy plays an important role in improving the prognosis of patients with lung cancer.[1,2] However, adverse effects associated with chemotherapy such as liver and kidney dysfunction, gastrointestinal mucosal damage, and bone marrow suppression cannot be ignored.[3-5] The most common and severe risk among patients who develop granulocytopenia after chemotherapy is infection following leukocytopenia, that is, febrile neutropenia (FN).[6,7] A previous study reported that approximately 86% of patients who died from FN were treated 2 hours after the onset of FN,[8] suggesting the importance of timely and effective treatment of FN. The Infectious Diseases Society of America guidelines recommend that a patient be administered an initial dose of antibacterial therapy within 1 hour after FN is diagnosed and be monitored for more than 4 hours before discharge from hospital. Therefore, treatment of granulocytopenia to avoid infection has become a concern after chemotherapy.[8]

In recent years, with the application of biological agents such as granulocyte colony–stimulating factor (G-CSF), the incidence of severe granulocytopenia after chemotherapy has decreased, and the prognosis of patients has improved.[9,10] However, because of the increase in chemotherapy cycles and implementation of the combination regimens, the incidence of severe granulocytopenia-related infection after chemotherapy remains high.[11] In addition, for a few patients with FN, standard treatment such as that using G-CSF or anti-infection drugs fails to increase the leukocyte levels of patients with severe granulocytopenia.[10] Therefore, other effective treatment of patients with severe granulocytopenia after chemotherapy warrant further investigation.

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Nutritional support therapy, as a part of cancer treatment, played a protective effect against bone marrow suppression after chemotherapy.[12,13] Early studies on nutritional intervention have focused on total parenteral nutrition (PN) because of its protective effect against bone marrow suppression after chemotherapy; however, limited benefits of total PN have been observed.[14,15] This could be attributed to the small cohort size (fewer than 40 patients) in these studies.[15-17] In addition, in some studies, total PN has failed to meet physiological demands, in addition to coming with high costs and numerous complications. Therefore, several clinicians have advocating replacing PN with enteral nutrition (EN) in clinical settings. However, EN may also fail to meet the needs of the bodies of critically ill patients, resulting in inadequate energy or protein intake.[18,19] For example, a multicentre clinical study reported that EN could provide more than 80% of energy and protein needs in only 25% of critically ill patients.[20] Considering that long-term nutritional deficiency may affect the prognosis of critically ill patients, supplemental parenteral nutrition (SPN) is used in some clinical practices.[21] In such cases, when EN is insufficient, some of the energy and protein requirements can be provided through PN.

At present, studies on SPN have been performed in critically ill patients with one or more organ failures.[20,22] Patients with cancer who develop life-threatening infections because of granulocytopenia after chemotherapy are categorised as critically ill patients, both European Society for Clinical Nutrition and Metabolism (ESPEN) and North American Enteral Parenteral Nutrition Association (ASPEN) guidelines recommends that SPN should be provided in critically cancer patients. However, the existing clinical trial data regarding the optimal timing of SPN intervention in such patients are inconclusive.[22-24] Therefore, it is of great clinical significance to explore the optimal timing of SPN in critically ill patients with cancer who develop severe granulocytopenia after chemotherapy. Prospective randomised controlled studies can provide high-level evidence to demonstrate whether early SPN improves the prognosis of patients with severe granulocytopenia after chemotherapy. However, severe granulocytopenia after chemotherapy may lead to life-threatening infections, which are difficult to conduct in randomized controlled study; poor patient compliance and reasonable ethics are also factors that should be considered. We report a retrospective study through which we sought to explore the effect of SPN timing in patients with lung cancer who developed severe granulocytopenia after chemotherapy.

METHODS

Patients and study design

A retrospective cohort study was conducted on severe granulocytopenia after chemotherapy in 288 patients with lung cancer who were admitted to our institute from January 2016 to February 2018. According to NCI-CTCAE version 4.0, Grade 3 and Grade 4 of granulocytopenia were considered severe granulocytopenia in our study. After evaluation, 182 patients were eligible for this study. They were classified into 2 groups, according to the timing of SPN intervention: early SPN (within 72 hours of development of granulocytopenia) and late SPN (after 72 hours of development of granulocytopenia). Patients in the early SPN group had leukopenia for a median of 1.94±0.80 days, whereas those in the late SPN group had leukopenia for a median of 5.80±1.24 days. Propensity score matching (PSM) was used to control the propensity bias of the 2 groups. We performed comparative analysis of the infection rate, absolute neutrophil count, length of hospital stay, and rate of chemotherapy completion of patients receiving early SPN and late SPN. This study was approved by the institutional review board of Chinese PLA General Hospital.

Inclusion and exclusion criteria

Patients older than 18 years who were diagnosed with lung cancer according to pathological guidelines, had severe granulocytopenia after chemotherapy, received SPN, and had an Eastern Cooperative Oncology Group (ECOG) score of 0–2 before chemotherapy were included. Patients who did not receive SPN when diagnosed with severe granulocytopenia after chemotherapy; received concurrent radiotherapy and chemotherapy; developed leukocytopenia or thrombocytopenia due to bone marrow invasion; failed to complete chemotherapy because of infection caused by severe anaemia or thrombocytopenia; had haematologic diseases such as myelodysplastic syndrome; or received treatment to increase white blood cell number, nonstandard nutritional treatment, or oral nutritional supplementation only were excluded.

Treatment of granulocytopenia

After chemotherapy, routine blood tests were performed every 3 days or at the onset of a fever. When patients developed severe granulocytopenia and their absolute number of neutrophils decreased below 1.0×10^9 cells/L, they were subcutaneously administered recombinant human G-CSF injection at a dose of 2–5 μg/kg per day. This treatment was discontinued when the neutrophil count reached 5.0×10^9 cells/L or when the white blood cell count exceeded 10.0×10^9 cells/L. The room was disinfected by UV rays; patients were instructed to gargle with nitrofurazone and administered an anti-infective agent such as moxifloxacin. Patients with fever were administered antibiotics such as third-generation cephalosporins or carbapenems. Those suspected to have fungal infections were administered an antifungal agent such as voriconazole or fluconazole. When the body temperature of a patient remained normal for more than 3 days and their absolute neutrophil count returned to the normal range, the anti-infection therapy was discontinued.

SPN methods and doses

The caloric targets were 35 kcal/kg per day for men and 30 kcal/kg per day for women. EN supply was recorded. PN (15–25 kcal/kg per day) was supplied when the EN provided less than 80% of the caloric target. Protein, carbohydrates, and fats contributed 20%, 40%, and 40%, respectively, of the parenteral calories. Electrolytes, trace elements, minerals, and vitamins were added as clinically appropriate. The specific implementation strategy was comprehensively evaluated according to the clinical condition and intestinal function of the patient. When the EN

met 80% of the caloric target or when patients could reach their caloric target by themselves, PN was discontinued.

Follow-up and data records

From the onset of severe granulocytopenia after chemotherapy, patients were followed up for 12 weeks (4 cycles of chemotherapy) or until death. A combination of telephone follow-up and systematic case registration follow-up was used.

Monitoring of study indicators

The primary indicators of the study were bacterial infection and fungal infection. Bacterial infection referred mainly to pulmonary infection and bacteraemia. Pulmonary infection could be clinically or aetiologically diagnosed according to pulmonary auscultation, chest X-ray, sputum culture, and blood culture. Bacteraemia could be diagnosed on the basis of clinical infection symptoms and blood culture. The diagnosis of fungal infection was based on detection of fungi in the sputum through microscopy or fungal culture (2 consecutive times) or from positive tests (2 consecutive times) for Glactomannan (GM) and (1,3) beta-D-glucan (G) test in blood samples.

The secondary indicators of the study were the duration for which the absolute neutrophil count was less than 1.0×10^9 cells/L, length of hospital stay, modality rate, and rate of chemotherapy (4 cycles) completion.

Statistical analysis

For α=0.05, 80% power, a 1:1 ratio, and 5% loss to follow-up, according to our previous retrospective studies (which have revealed that early SPN could reduce the likelihood of infection in patients with lung cancer by 10% compared with that in patients who receive late SPN), the minimal sample size was estimated to be 91 patients per group. The time from onset of severe granulocytopenia to infection was recorded, and the incidence of infection was analysed among all patients who completed the follow-up.

All statistical analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Categorical variables are described as percentages and were compared using the chi square and Fisher exact tests. Continuous variables are described as mean ± standard deviation (SD) and were compared using the 2 sample Student t test or ANOVA, as appropriate.

Univariate analysis was used to compare each subgroup between the groups. To determine which subgroup would benefit more from SPN, several significant subgroups in the univariate analysis or those considered clinically important were further analysed to estimate ORs with 95% CIs in the binary logistic regression model for granulocytopenia-related infection. Interaction logistic analysis was conducted according to patient age and factors determined to be significant in univariate analysis or those considered clinically important. A two-tailed $p<0.05$ was considered statistically significant.

RESULTS

Study design and workflow overview

We reviewed the clinical data of 288 patients with lung cancer who developed myelosuppression after chemotherapy in our department from January 2016 to February 2018. A total of 103 patients were excluded owing to reasons such as having Grade 1 or Grade 2 granulocytopenia (n=88) or being unfit for treatment (n=6); 3 of the remaining 185 patients were excluded because they were lost to follow-up.

Patients who received SPN within 72 hours of diagnosis of severe granulocytopenia after chemotherapy were classified as the early SPN group (n=92), and those who received SPN after more than 72 hours of diagnosis were classified as the late SPN group (n=90). The 182 eligible patients consisted of 90 men and 92 women, with a median age of 64 (range, 45–77) years. The study design and patient selection process are demonstrated in Figure 1.

At baseline, the following clinical characteristics of the patients in the 2 treatment groups did not differ significantly: age, gender, ECOG performance score, nutritional risk screening-2002 (NRS-2002) score, history of myelosuppression (pre-myelosuppression), history of chemotherapy (pre-chemotherapy), history of prophylactic use of G-CSF, weight loss, and anti-tumour therapeutic agent (Table 1). In addition, the energy and protein intake per day by patients in the early SPN group and those in the late SPN group was similar, as shown in Table 2. Therefore, the groups were comparable in terms of these parameters.

Different incidence rates of infections between the early SPN and late SPN groups

The duration of observation was the same for the early and late SPN groups. With the onset of severe granulocytopenia as the starting point, the follow-up period was 4 chemotherapy cycles (12 weeks). Among patients with lung cancer with severe granulocytopenia after chemotherapy, the incidence rate of bacterial infection was significantly lower among patients who received early SPN than among patients who received late SPN (8.7% vs 20.0%, χ^2=4.748, p=0.029, Figure 2). The rate of fungal infection was also lower among patients who received early SPN than among those who received late SPN (3.3% vs 11.1%, χ^2=4.227, p=0.04). However, in terms of mortality, although early SPN reduced the mortality related to granulocytopenia after chemotherapy, no significant difference was observed between the groups (4.3% vs 6.7%, χ^2=0.47, p=0.49).

Differences in absolute neutrophil count, hospitalisation, and chemotherapy completion rate between the early SPN and late SPN groups

Compared to late SPN intervention, early SPN significantly shortened the duration of absolute neutrophil count less than 1.0×10^9 cells/L (4.50±2.63 days vs 6.10±3.15 days, t test, $p<0.001$, Figure 3A). The mean hospital stay in the early SPN group was significantly shorter than that in the late SPN group (8.35±4.10 days vs 10.22±3.72 days, t test, p=0.001, Figure 3B). In addition, early SPN was significantly associated with a higher rate of completion of 4 cycles of chemotherapy, compared with late SPN (75.0% vs 57.8%, χ^2=6.056, p=0.01, Figure 3C).

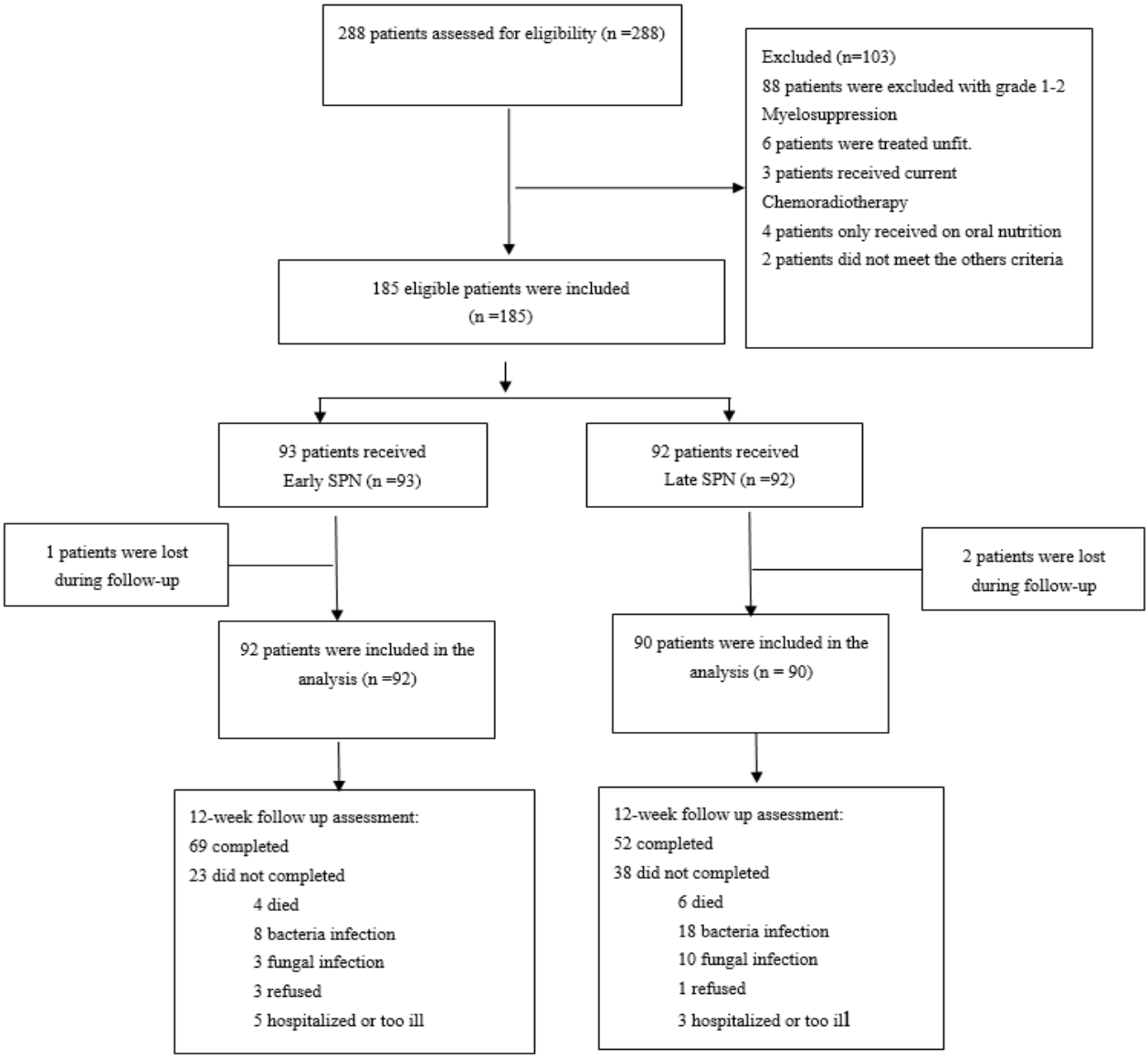
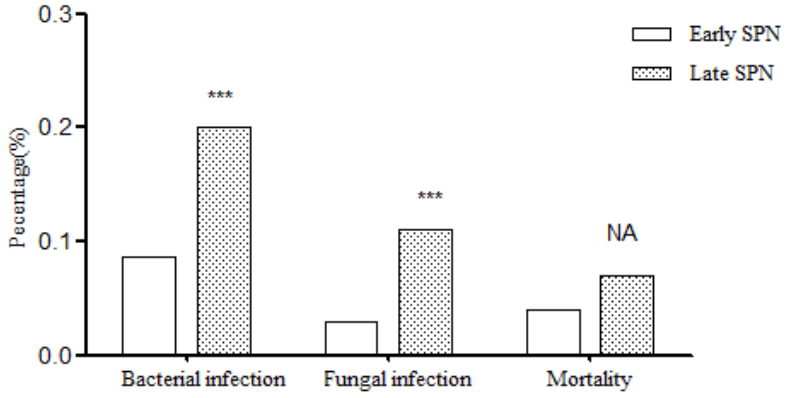


Figure 1. Flow diagram of patient enrolment. A total of 288 patients with lung cancer who developed granulocytopaenia after chemotherapy were assessed on admission to the hospital; 106 patients were excluded as they did not satisfy the inclusion criteria or because they were lost to follow-up. Finally, a total of 182 patients were observed



n (%)	Early SPN N=92	Late SPN N=90	χ^2	p
Bacterial infection	8(8.7%)	18(20%)	4.748	0.029
Fungal infection	3(3.3%)	10(11.1%)	4.227	0.040
Mortality	4(4.3%)	6(6.7%)	0.471	0.492

Figure 2. Comparison of bacterial infection rate, fungal infection rate, and mortality rate between patients receiving early-initiated SPN and late-initiated SPN. Categorical variables were described as percentages and compared using Chi square test ($^{***}p<0.05$).

Table 1. Baseline patient characteristics

Characteristic	n	Early SPN (n=92)	Late SPN (n=90)	χ^2 or t test	*p* value
Mean age (years), mean±SD		61.6±7.65	63.4±6.06	1.83	0.068
≥65, n (%)	90	43 (46.7)	37 (41.1)	0.59	0.459
<65, n (%)	92	49 (53.3)	53 (58.9)		
Gender, n (%)					
Female	92	44 (47.8)	48 (53.3)	0.55	0.463
Male	90	48 (52.2)	42 (46.7)		
ECOG, n (%)					
0	15	10 (10.9)	5 (5.6)	2.15	0.341
1	126	60 (65.2)	66 (73.3)		
2	41	22 (23.9)	19 (21.1)		
NRS 2002, n (%)					
1	86	40 (43.5)	46 (51.1)	2.22	0.330
2	51	25 (27.2)	26 (28.9)		
≥3	45	27 (29.3)	18 (20.0)		
Histology, n (%)					
Adenocarcinoma	57	26 (28.3)	31 (34.4)	1.76	0.414
Squamous	48	28 (30.4)	20 (22.2)		
SCLC	77	38 (41.3)	39 (43.3)		
Pre-myelosuppression, n (%)					
No	82	43 (46.7)	39 (43.3)	0.21	0.644
Yes	100	49 (53.3)	51 (56.7)		
Pre-chemotherapy, n (%)					
No	63	35 (38.0)	28 (31.1)	0.97	0.326
Yes	119	57 (62.0)	62 (68.9)		
Prophylactic use of G-CSF, n (%)					
No	87	40 (43.5)	47 (52.2)	1.39	0.238
Yes	95	52 (56.5)	43 (47.8)		
Weight loss†, n (%)					
No	103	53 (57.6)	50 (55.6)	0.08	0.780
Yes	79	39 (42.4)	40 (44.4)		
Anti-tumor therapeutic agents, n (%)					
Single chemotherapy	24	11 (12.0)	13 (14.4)	0.26	0.878
Double chemotherapy	138	71 (77.2)	67 (74.4)		
Multiple hemotherapy	20	10 (10.9)	10 (11.1)		

SPN: supplemental parenteral nutrition; ECOG: Eastern Cooperative Oncology Group; NRS 2002: nutritional risk screening-2002; SCLC: small cell lung cancer.
†Weight loss was defined as loss of over 5% of weight within 3 months.

Table 2. Energy and protein intake per day of the early SPN and late SPN groups

	Early SPN (N=92)	Late SPN (N=90)	t test	*p* value
EN				
Energy (kcal/kg.day)	17.4±2.6	17.5±2.2	0.35	0.731
Protein (g/kg.day)	0.7±0.1	0.7±0.1	0.64	0.526
SPN				
Energy (kcal/kg.day)	15.5±2.8	15.4±2.7	0.19	0.846
Protein (g/kg.day)	0.6±0.1	0.6±0.1	0.95	0.343
Total				
Energy (kcal/kg.day)	32.8 ±2.4	32.9±2.3	0.13	0.894
Protein (g/kg.day)	1.3±0.1	1.3±0.1	1.58	0.115

EN: enteral nutrition; SPN: supplemental parenteral nutrition.
Values are presented as mean±SD.

Multivariate analysis of factors associated with infection rate

After preliminary results indicating that early initiation of SPN can reduce the rate of infection among patients with lung cancer who develop severe granulocytopenia after chemotherapy, we attempted to determine which patient subpopulations would benefit more from early SPN than from late SPN.

To explore the factors potentially associated with the incidence rates of infections, we conducted univariate analyses between the early SPN and late SPN groups. Table 3 displays the statistic value of clinical characteristics associated with infection rates. Lower infection rates were significantly correlated with an NRS-2002 score of

Table 3. Univariate and multivariate analysis of factors associated with infection rate according to baseline characteristics

	Early SPN		Late SPN		Statistic	*p*	Binary logistic regression		
	Events	Total	Events	Total	value	value	OR	95% CI	*p* value
Age									
≥65 years	6	43	11	37	2.96	0.085			
<65 years	2	49	7	53	2.64	0.104			
Sex									
Male	4	44	9	48	1.77	0.184			
Female	4	48	9	42	3.11	0.078			
ECOG Score									
1	4	60	12	66	3.76	0.053			
2	4	22	6	19	0.99	0.469	0.72	0.22, 2.31	0.578
NRS2002									
1	1	40	3	46	0.78	0.377	0.56	0.17, 1.82	0.332
2	1	25	9	26	7.58	0.011	0.18	0.04, 0.76	0.019
3	6	27	6	18	0.68	0.499	4.32	0.61, 30.7	0.144
Histology									
Adenocarcinoma	3	26	6	31	0.65	0.488			
Squamous	2	28	3	20	0.77	0.636			
SCLC	3	38	9	39	3.37	0.066			
Pre-myelosuppression									
No	1	43	1	39	0.004	1.000			
Yes	7	49	17	51	4.97	0.026	0.51	0.07, 3.49	0.489
Pre-chemotherapy									
No	1	35	1	28	0.03	1.000			
Yes	7	57	17	62	4.23	0.040	0.54	0.08, 3.55	0.517
prophylactic use of G-CSF									
No	5	40	3	47	0.97	0.462			
Yes	3	52	15	43	13.0	0.000	0.45	0.16, 1.28	0.132
Weight loss									
No	1	53	3	50	1.17	0.353			
Yes	7	39	15	40	3.76	0.053			
Chemotherapy									
Single	0	11	3	13	2.90	0.223			
Double	5	71	11	67	2.96	0.086			
Multiple	3	10	4	10	0.22	1.000			

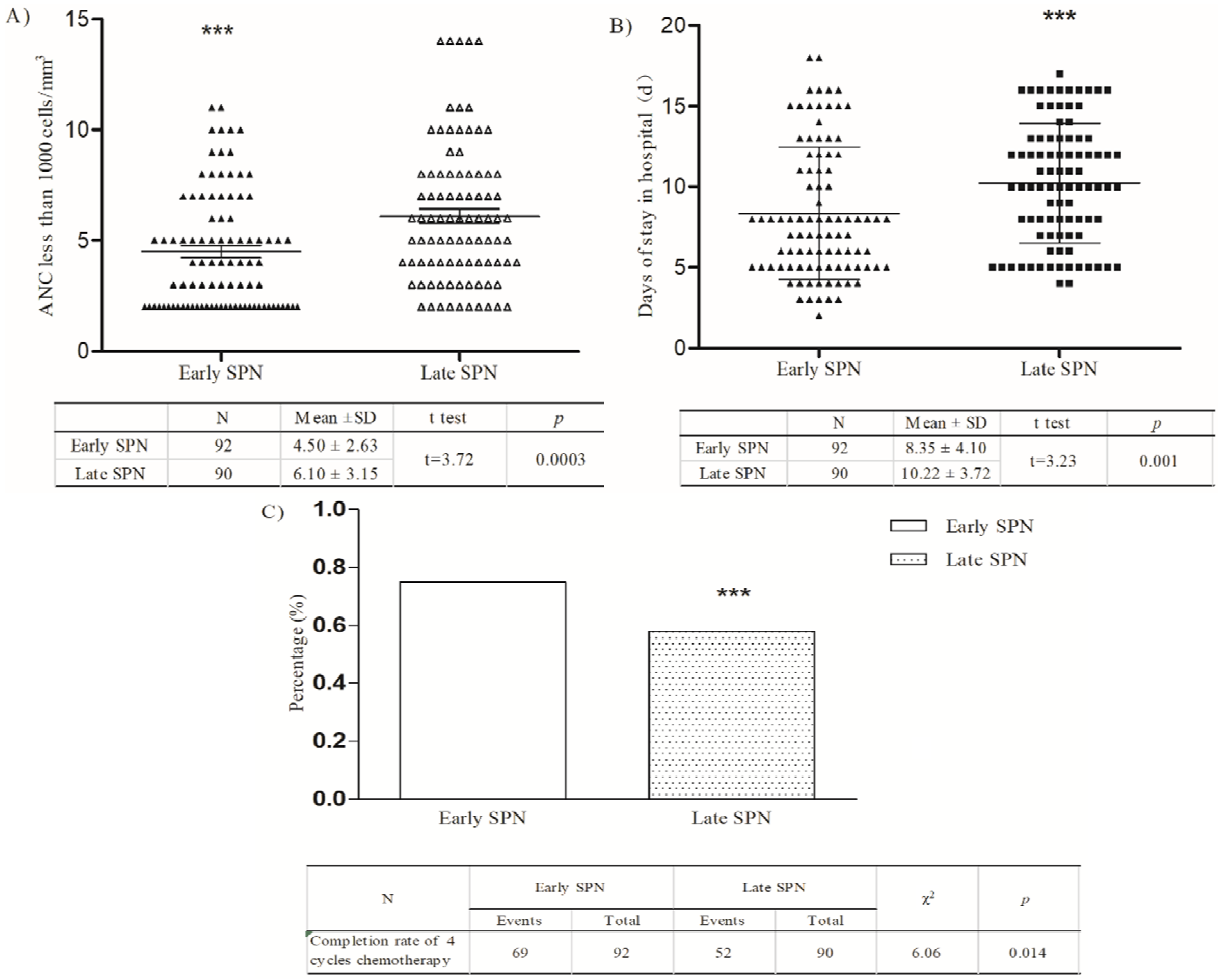
SPN: supplemental parenteral nutrition; ECOG: Eastern Cooperative Oncology Group; NRS 2002: nutritional risk screening-2002; G-CSF: granulocyte colony stimulating factor.

2 (χ^2=7.578, p=0.011), pre-myelosuppression (χ^2=4.971, p=0.026), pre-chemotherapy (χ^2=4.227, p=0.04), and prophylactic use of G-CSF (χ^2=12.991, p=0.000) in the early SPN group. Multivariate logistic regression analysis indicated that patients with an NRS-2002 score of 2 (OR=0.184; 95% CI, 0.045, 0.758; p=0.019) benefit from early SPN. Interaction logistic regression analysis showed that early SPN was associated with a significantly lower incidence of infection in older patients with lung cancer who had a history of granulocytopenia.

DISCUSSION

In this study, we compared the clinical benefits of early SPN (within 72 hours of diagnosis of granulocytopenia) with those of late SPN (over 72 hours after diagnosis of granulocytopenia) in 182 eligible patients with lung cancer who developed chemotherapy-induced severe granulocytopenia and who received insufficient nutrition through EN. We found that early initiation of SPN was associated with a lower risk of infection that late initiation of SPN. In addition, compared with late SPN, early SPN was associated with a higher rate of completion of chemotherapy and shorter hospital stays and leukocyte recovery periods. Moreover, we performed a relative risk analysis and stratified patients to determine which patient groups would receive more benefits from early SPN than from late SPN.

Studies on nutrition supplementation have been performed in critically ill patients with one or more organ failures.[20,24-28] Most patients who developed severe granulocytopenia after chemotherapy in our study did not have organ failure or any other serious complications. Therefore, our patients were relatively representative because the biases introduced by complications and poor homogeneity between samples were minimised. In addition, unlike previous studies,[29,30] we used baseline NRS-2002 score and PSM to control bias between the groups;[31] thus, our conclusions should be sufficiently reliable. With regard to the timing of SPN initiation, the ESPEN recommends that SPN be started within 2 days; however, the North American Enteral Parenteral Nutrition Association guidelines recommend that PN be initiated after 7 days if EN fails to achieve the caloric target.[32,33] However, there is no definite time optimal for starting SPN. In our study, we considered the aforementioned timing recommendations and selected 3 days as the cut-off between early SPN and late SPN.



	N	Mean ±SD	t test	*p*
Early SPN	92	4.50 ± 2.63	t=3.72	0.0003
Late SPN	90	6.10 ± 3.15		

	N	Mean + SD	t test	*p*
Early SPN	92	8.35 ± 4.10	t=3.23	0.001
Late SPN	90	10.22 ± 3.72		

N	Early SPN		Late SPN		χ^2	*p*
	Events	Total	Events	Total		
Completion rate of 4 cycles chemotherapy	69	92	52	90	6.06	0.014

Figure 3. Secondary outcomes between patients receiving early-initiated SPN and late-initiated SPN. (A) Differences in absolute neutrophil count between early SPN and late SPN groups. Values are presented as mean ± SD. (B) Differences in hospital stays between the groups. Values are presented as mean ± SD. (C) Differences in the rates of completion of four cycles of chemotherapy between the groups. Comparisons between the different sub-groups were performed using Chi square test (***p<0.05).

The optimal timing of SPN initiation in patients whose caloric targets cannot be met by EN alone remains controversial. Wang et al reported that compared with early initiation of SPN, late initiation of SPN increased the incidence of nosocomial infections in critically ill children, consistent with our findings.[29] However, Casaer et al reported that among patients who were receiving insufficient EN, those in a late SPN group had lower risk infection (22.8% vs 26.2%; p=0.008) and shorter median stays in the ICU (3 vs 4 days; p=0.02) compared with patients from their early SPN initiation group.[25,34] The discrepancies between the results of these studies and ours may be attributed to several factors. First, in the study by Casaer et al, early SPN was initiated within 48 hours of onset of severe granulocytopenia, and late SPN was initiated after 8 days. The period between day 2 and day 8, which might affect the outcome, was not evaluated. Second, critically ill patients typically have complex diseases and complications, which may introduce bias into the results. However, in our cohort, the proportion of such patients was only approximately 20%, and the effects on the conclusions were minimised. Third, in the study by Casaer et al, the proportion of patients with sepsis was 20%, and infection itself may affect the development of complications; moreover, the nutritional risk scores of the patients were high (3–7 points); therefore, the representativeness of the patients was poor. According to the aforementioned results, we suggest that the clinical advantage of early over late SPN should be confirmed in larger cohorts with more uniform patient characteristics and minimal complication bias.

Subgroup analysis indicated that compared with late SPN, early SPN could reduce the infection rate in patients with severe granulocytopenia after chemotherapy in patients with an NRS-2002 score of 2, with chemotherapy history, with history of G-CSF application, or using a single antitumour agent. Multivariate logistic regression analysis confirmed that the subgroup of patients with an NRS-2002 score of 2 benefited from early SPN.

The NRS-2002 score includes not only weight loss but also food intake and the status of the disease itself. Therefore, it is recommended by the ESPEN for risk scoring in cancer. Compared with late initiation of SPN, early initiation of SPN was associated with a lower incidence of granulocytopenia-associated infections in patients with an NRS-2002 score of 2 in our cohort. One possible reason is that patients with an NRS-2002 score of 1 had a relatively low malnutrition risk and may not have required SPN. The risk of bacterial infection after chemotherapy was relatively high among patients with an NRS-2002 score of ≥3; therefore, the infection rates of patients receiving early SPN and those receiving late SPN did not

differ significantly. The risk of malnutrition in patients with an NRS-2002 score of 2 was moderate, and their infection rates might be sensitive to the timing of SPN initiation.

This study used logistic regression analysis to analyse possible interactions between subgroups. Although there was no benefit of early SPN in elderly patients or in those with previous granulocytopenia, the interaction analysis suggested a significant association between lung cancer with previous granulocytopenia and elderly patients. We found that early SPN could reduce the incidence of lung cancer–related infections in elderly patients with severe granulocytopenia. This could be attributed to the relatively poor bone marrow reserve function among elderly patients with lung cancer. The recovery time after granulocytopenia is relatively long, and granulocytopenia-related infections are common during this period. Therefore, the interactions between these patients should be considered to improve the diagnosis and treatment of severe granulocytopenia after chemotherapy.

The effects of early and late SPN intervention on the mortality of patients with lung cancer who develop granulocytopenia after chemotherapy were not significantly different. Our observation was echoed by Kutsogiannis et al, who reported that compared with late SPN, early SPN slightly reduced the mortality rate of patients undergoing mechanical ventilation; however, the difference was not statistically significant.[35] The result was consistent with our observation. Many factors could affect the outcome of mortality of patients with granulocytopenia. A possible reason for this is that the factors associated with mortality include not only leukocytopenia-associated infection but also tumour progression and numerous other confounding factors, whereas nutritional support contributes mainly to the improvement of leukocytopenia. Another possible reason is that the cohort size in our study was small, and the number of deaths was limited. Therefore, whether the timing of SPN administration affects mortality rate should be further investigated in larger cohorts.

Our study has several limitations. First, the population included mainly patients with chemotherapy-induced severe granulocytopenia; thus, its clinical value is not applicable to all patients with myelosuppression. Second, functional supplements such as n-3 fatty acids and alanyl glutamine in parenteral nutrition have been reported to have different anti-inflammatory effects and may have introduced bias into the clinical outcomes of our patients. Third, this study was a single-centre study and thus may have had a central effect; therefore, validation of our results in a multicentre randomised clinical trial is warranted.

In conclusion, early SPN could reduce the incidence of granulocytopenia-related infections, improve the likelihood of chemotherapy completion, reduce the recovery time of leukocytes, and shorten hospital stays. Nutritional risk assessment should be performed in patients with lung cancer who develop chemotherapy-induced severe granulocytopenia. Exploration and research in clinical practice are warranted to confirm the benefits of early SPN.

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AUTHOR DISCLOSURES
The authors declare no conflict of interest.

REFERENCES

1. Nagasaka M, Gadgeel SM. Role of chemotherapy and targeted therapy in early-stage non-small cell lung cancer. Expert Rev Anticancer Ther. 2018;18:63-70. doi: 10.1080/14737140.2018.1409624.
2. Rossi A, Di Maio M. Platinum-based chemotherapy in advanced non-small-cell lung cancer: optimal number of treatment cycles. Expert Rev Anticancer Ther. 2016;16:653-60. doi: 10.1586/14737140.2016.1170596.
3. Okada T, Nakajima Y, Nishikage T, Ryotokuji T, Miyawaki Y, Hoshino A et al. A prospective study of nutritional supplementation for preventing oral mucositis in cancer patients receiving chemotherapy. Asia Pac J Clin Nutr. 2017;26:42-8. doi: 10.6133/apjcn.112015.03.
4. Opanga L, Mulaku MN, Opanga SA, Godman B, Kurdi A. Adverse effects of chemotherapy and their management in Pediatric patients with non-Hodgkin's lymphoma in Kenya: A descriptive, situation analysis study. Expert Rev Anticancer Ther. 2019;19:423-30. doi: 10.1080/14737140.2019.1606717.
5. Phaibulvatanapong E, Srinonprasert V, Ithimakin S. Risk factors for chemotherapy-related toxicity and adverse events in elderly Thai cancer patients: a prospective study. Oncology. 2018;94:149-60. doi: 10.1159/000485078.
6. Do T, MedhekarR, Bhat R, Chen H, Niravath P, Trivedi MV. The risk of febrile neutropenia and need for G-CSF primary prophylaxis with the docetaxel and cyclophosphamide regimen in early-stage breast cancer patients: a meta-analysis. Breast Cancer Res Treat. 2015;153:591-7. doi: 10.1007/s10549-015-3531-z.
7. Chan A, Fu WH, Shih V, Coyuco JC, Tan SH, Ng R. Impact of colony-stimulating factors to reduce febrile neutropenic events in breast cancer patients receiving docetaxel plus cyclophosphamide chemotherapy. Support Care Cancer. 2011;19:497-504. doi: 10.1007/s00520-010-0843-8.
8. Taplitz RA, Kennedy EB, Bow EJ, Crews J, Gleason C, Hawley DK et al. Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America Clinical Practice Guideline Update. J Clin Oncol. 2018;36:1443-53. doi: 10.1200/JCO.2017.77.6211.
9. Renner P, Milazzo S, Liu JP, Zwahlen M, Birkmann J, Horneber M. Primary prophylactic colony-stimulating factors for the prevention of chemotherapy-induced febrile neutropenia in breast cancer patients. Cochrane Database Syst Rev. 2012;10:CD007913. doi: 10.1002/14651858.CD007913.pub2.
10. Skoetz N, Bohlius J, Engert A, Monsef I, Blank O, Vehreschild JJ. Prophylactic antibiotics or G(M)-CSF for the prevention of infections and improvement of survival in cancer patients receiving myelotoxic chemotherapy. Cochrane Database Syst Rev. 2015;12:CD007107. doi: 10.1002/14651858.CD007107.pub3.
11. Smith TJ, Bohlke K, Lyman GH, Carson KR, Crawford J, Cross SJ et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2015;33:3199-212. doi: 10.1200/JCO.2015.62.3488.
12. Liang R, Chen GY, Fu SX, Zhong J, Ma Y. Benefit of oral nutritional supplements for children with acute lymphoblastic leukaemia during remission-induction chemotherapy: a quasi-experimental study. Asia Pac J Clin Nutr. 2018;27:144-7. doi: 10.6133 /apjcn.032017.04.

13. Virizuela JA, Camblor-Álvarez M, Luengo-Pérez LM, Grande E, Álvarez-Hernández J, Sendrós-Madroño MJ et al. Nutritional support and parenteral nutrition in cancer patients: an expert consensus report. Clin Transl Oncol. 2018;20:619-29. doi: 10.1007/s12094-017-1757-4.
14. Paccagnella A, Morassutti I, Rosti G. Nutritional intervention for improving treatment tolerance in cancer patients. Curr Opin Oncol. 2011;23:322-30. doi: 10.1097/ CCO.0b013e3283479c66.
15. Bossola M. Nutritional interventions in head and neck cancer patients undergoing chemoradiotherapy: a narrative review. Nutrients. 2015;7:265-76. doi: 10.3390/nu7010265.
16. Ward EJ, Henry LM, Friend AJ, Wilkins S, Phillips RS. Nutritional support in children and young people with cancer undergoing chemotherapy. Cochrane Database Syst Rev. 2015;8:CD003298. doi: 10.1002/14651858.CD003298. pub3.
17. Akutsu Y, Kono T, Uesato M, Hoshino I, Murakami K, Fujishiro T et al. Are additional trace elements necessary in total parenteral nutrition for patients with esophageal cancer receiving cisplatin-based chemotherapy? Biol Trace Elem Res. 2012;150:109-15. doi: 10.1007/s12011-012-9513-7.
18. Cotogni P. Enteral versus parenteral nutrition in cancer patients: evidences and controversies. Ann Palliat Med. 2016;5:42-9. doi: 10.3978/j.issn.2224-5820. 2016.01.05.
19. Chow R, Bruera E, Chiu L, Chow S, Chiu N, Lam H et al. Enteral and parenteral nutrition in cancer patients: a systematic review and meta-analysis. Ann Palliat Med. 2016;5:30-41. doi: 10.3978/j.issn.2224-5820.2016.01.01.
20. Heidegger CP, Berger MM, Graf S, Zingg W, Darmon P, Costanza MC et al. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. Lancet. 2013;381:385-93. doi: 10.1016/S0140-6736(12)61351-8.
21. Berger MM, Achamrah N, Pichard C. Parenteral nutrition in intensive care patients: medicoeconomic aspects. Curr Opin Clin Nutr Metab Care. 2018 ;21:223-7. doi: 10.1097/MCO. 0000000000000454.
22. Lazaro-Martin NI, Catalan-Gonzalez M, Garcia-Fuentes C, Terceros-Almanza L, Montejo-Gonzalez JC. Analysis of the nutritional management practices in intensive care: Identification of needs for improvement. Med Intensiva. 2015;39:530-6. doi: 10.1016/ j.medin.2015.04.010.
23. Lewis SR, Schofield-Robinson OJ, Alderson P, Smith AF. Enteral versus parenteral nutrition and enteral versus a combination of enteral and parenteral nutrition for adults in the intensive care unit. Cochrane Database Syst Rev. 2018;6:CD012276. doi: 10.1002/ 14651858.CD012276.pub 2.
24. Wischmeyer PE, Hasselmann M, Kummerlen C, Kozar R, Kutsogiannis DJ, Karvellas CJ et al. A randomized trial of supplemental parenteral nutrition in underweight and overweight critically ill patients: the TOP-UP pilot trial. Crit Care. 2017;21:142. doi: 10.1186/ s13054-017-1736-8.
25. Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med. 2011;365:506-17. doi: 10. 1056/NEJMoa1102662.
26. Li Y, Huang Y. Early versus late parenteral nutrition in critically ill children. N Engl J Med. 2016; 75:384-5. doi: 10.1056/NEJMc1605395.
27. Casaer MP, Hermans G, Wilmer A, Van den Berghe G. Impact of early parenteral nutrition completing enteral nutrition in adult critically ill patients (EPaNIC trial): a study protocol and statistical analysis plan for a randomized controlled trial. Trials. 2011;12:21. doi: 10.1186/1745-6215-12-21.
28. Allingstrup MJ, Kondrup J, Wiis J, Claudius C, Pedersen UG, Hein-Rasmussen R et al. Early goal-directed nutrition versus standard of care in adult intensive care patients: the single-centre, randomised, outcome assessor-blinded EAT-ICU trial. Intensive Care Med. 2017;43:1637-47. doi: 10. 1007/s00134-017-4880-3.
29. Wang D, Lai X, Liu C, Xiong Y, Zhang X. Influence of supplemental parenteral nutrition approach on nosocomial infection in pediatric intensive care unit of Emergency Department: a retrospective study. Nutr J. 2015;14:103. doi: 10.1186/s12937-015-0094-0.
30. Gavri C, Kokkoris S, Vasileiadis I, Oeconomopoulou AC, Kotanidou A, Nanas S et al. Route of nutrition and risk of blood stream infections in critically ill patients; a comparative study. Clin Nutr ESPEN. 2016;12:e14-e9. doi: 10.1016/j.clnesp.2016.01.002.
31. Huber S, Dietrich JF, Nagengast B, Moeller K. Using propensity score matching to construct experimental stimuli. Behav Res Methods. 2017;49:1107-19. doi: 10.3758/s1342 8-016-0771-8.
32. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr. 2017;36:11-48. doi: 10.1016/j.clnu.2016. 07.015.
33. Huhmann MB, August DA. Review of American Society for Parenteral and Enteral Nutrition (ASPEN) clinical guidelines for nutrition support in cancer patients: nutrition screening and assessment. Nutr Clin Pract. 2008; 23:182-8. doi: 10.1177/0884533608314530.
34. Cove ME, Pinsky MR. Early or late parenteral nutrition: ASPEN vs. ESPEN. Crit Care. 2011;15:317. doi: 10.1186/ cc10591.
35. Kutsogiannis J, Alberda C, Gramlich L, Cahill NE, Wang M, Day AG et al. Early use of supplemental parenteral nutrition in critically ill patients: results of an international multicenter observational study. Crit Care Med. 2011;39: 2691-9. doi: 10.1097/CCM.0b013e3182282a83.