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Incident hyperglycemia, parenteral nutrition administration and adverse outcomes in patients with myeloma admitted for initial autologous stem cell transplant

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Abstract

Parenteral nutrition (PN) exacerbates hyperglycemia, which is associated with increased morbidity and mortality in various cancer populations. Using a retrospective design, we examined incident hyperglycemia in PN and non-PN recipients and the associations with clinical events and 5-year survival in a cohort treated for myeloma with melphalan and auto-SCT (n=112). Clinical comparisons were made at admission, and “before” and “after” initiating PN to discern differences and temporality. Actual infusion times were used for PN patients; timeframes based on mean PN infusion days were created for the non-PN recipients. Oral intake was lower “before” in PN vs. non-PN patients (p=<0.001); however, no differences in mucositis, emesis, infections or transfusions were detected “before.” Incident hyperglycemia (≥7.0 mmol/L) was significant

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"after" PN initiation, and PN recipients experienced delays in WBC ($p<0.05$) and platelet engraftment ($p= 0.009$) and required significantly greater RBC ($p=0.0014$) and platelet ($p=0.001$) support "after" than non-PN patients. Neutropenic fever and longer hospital stay were more frequent among PN vs. non-PN recipients ($p<0.001$). Differences in 5-year mortality were not apparent. Findings fail to support clinical benefits of PN administration during auto-SCT for myeloma. Further study is needed to discern if hyperglycemia or feeding *per se* was deleterious in this patient population.

Keywords

parenteral nutrition; myeloma; auto-SCT; hyperglycemia; feeding; nutrition support

INTRODUCTION

Despite the discovery of novel agents for the treatment of myeloma over the past decade[1], high dose chemotherapy followed by auto-SCT remains a front-line treatment option[2, 3]. Consequently, the combination of disease burden and the intensity of transplant therapy results in a multitude of medical, physical and supportive care challenges for these unique survivors. Little is known about the nutritional aspects of their care prior to, during or following SCT, despite the high volume of myeloma patients transplanted annually[4]. Often during transplantation, nutrition impact symptoms arise (ie, anorexia, nausea, vomiting, xerostomia). Parenteral nutrition (PN) is provided under the assumptions that it provides essential substrates to the host with a therapeutic goal of preventing malnutrition[5].

Over a decade ago, Van den Berghe et al illustrated the dramatic effects of acute hyperglycemia management (blood glucose ≥ 6.1 mmol/L) on hospital morbidity and mortality for critically ill surgical patients, irrespective of diabetes[6]. Since this time, considerable clinical and research efforts in a variety of hospitalized patient populations have been pursued to improve hyperglycemia management and consequently acute hospital outcomes. PN, a supportive care therapy commonly utilized in the SCT patient population, is associated with hyperglycemia[7-9]. In a heterogenous cohort of SCT recipients, those who received PN experienced a higher incidence of infection and significant delays in WBC and platelet engraftment for autologous ($p=0.01$) and allogeneic ($p=0.02$) donor types when compared to non-PN recipients[10]. More recent studies now show that acute hyperglycemia in patients receiving various forms of cancer treatment is associated with increased hospital mortality[11], organ dysfunction[12], and also decreased overall survival[12, 13], symbolizing both, acute and residual effects. The reasons behind these findings remain unclear; however, converging theories support that hyperglycemia during induction therapy and/or neutropenia may have a direct role on immune function, tumor response and inflammation; thus, predisposing individuals to subsequent infections and recurrence[13]. Currently, the implications of hyperglycemia in the myeloma SCT patient population are largely unknown. Therefore, the purpose of this paper was to characterize glycemic control in this predominant SCT population and to explore the associations between hyperglycemia, common transplant endpoints and survival. It was hypothesized that PN administration

would be associated with a higher incidence of hyperglycemia, prolonged engraftment and decreased 5-year survival in this homogeneous group.

MATERIALS AND METHODS

Study design, patient population and sampling procedure

A subset of patients from a previous retrospective cohort (n=357) was examined for this follow-up study[10]. Patients with myeloma were specifically chosen because: a) myeloma is the leading indication for SCT, b) PN exposure was frequent, providing the opportunity to efficiently exam the incidence of hyperglycemia in PN recipients vs. non-recipients, and c) 5-year survival rate was estimated at only 41%[14], enabling detection of differences in mortality rates. To permit clinical comparisons regarding the outcomes of interest, patient were required to be diagnosed with myeloma, ≥18 years of age, admitted for an initial auto-SCT, free of documented infection and not receiving home PN. These criteria yielded 112 patients from the original cohort for these analyses. Ethical approval for this study was granted from the Institutional Review Boards at both university transplant centers.

Data collection

Computerized and hard-copy medical records were reviewed for patient information regarding age, sex, race/ethnicity, medical and/or surgical history, admission performance scale measure, conditioning chemotherapy, laboratory results, admission anthropometrics, PN prescription, daily body weight, maximum body temperatures, the daily occurrence of mucositis and emesis (yes/no) from admission to discharge, RBC and/or platelet transfusions, the number of CD34+ cells transplanted and stem cell source. Because calorie counts data were not available, oral intake (yes/no) was crudely assessed as ≥ 500 mL any oral intake (eg, juice, water, oral supplements) or <500 mL any oral intake per day utilizing nursing intake and output graphics. Data on diarrhea was inconsistently recorded and therefore, not collected. Blood glucose was recorded once per day from the first morning venous blood draw (2:00-6:00 am) to achieve uniformity among patients, minimizing the influence of oral intake and avoiding measurements occurring more frequently among patients prone to hyperglycemia. Body weight and height were used to calculate admission body mass index (BMI) (weight (kg) / [height $(m)^2$]) and to classify obesity. WBC engraftment was defined as the number of days between transplant day 0 and the first day of 3 consecutive days that the absolute neutrophil count was $>.5 \times 10^9$/L. Platelet engraftment occurred when platelets were $>50 \times 10^9$/L without exogenous platelet support >7 days, respectively.

For these follow up analyses, medical records were retrieved and reviewed for additional information concerning blood glucose management (e.g., oral agents and insulin). Information regarding mortality was retrieved from the institution-specific SCT databases, which are updated biannually by matching social security numbers with results from the national death index.

Comparability between PN recipients and non-recipients

No protocols or standardized approaches were formally employed at either institution to determine when to initiate or to discontinue PN. Due to the recognition that patients who received PN may be clinically dissimilar from non-PN recipients and thus have different outcomes, several analytical strategies were undertaken. First, strict eligibility criteria were employed that excluded potentially sicker patients, removing those with pre-existing infections, varying conditioning chemotherapies and diagnoses, and higher risk donor types (eg, allogeneic, matched unrelated donors.) Second, clinical characteristics were examined at baseline between feeding groups that would potentially explain fundamental differences that would influence outcomes (eg, age, comorbidities). Third, “before” and “after” timeframes were created to help discern temporal changes in blood glucose values and therefore clinical outcomes in the time preceding PN (“before”) vs. the time following PN (“after”) administration. For PN recipients, the actual number of hospital days before and after PN were utilized; however, for non-PN recipients equivalent timeframes were created based on the average number of days prior to and during actual PN administration. Because the average PN patient with myeloma received PN on hospital day 10 and discontinued PN on hospital day 19, the “before” timeframe corresponded to hospital days 1-9 whereas the “after” timeframe reflected hospital days 10-19 for non-PN recipients. Additionally, neither adult transplant center utilized enteral feedings or had dedicated lines for PN administration due to the high volume of infusions required in this population.

Statistical Analyses

Hyperglycemia (defined as blood glucose ≥ 7.0 mmol/L) was the primary outcome of interest. Engraftment, blood product support, infections, neutropenic fever, length of hospitalization and 5-year survival were analyzed as secondary outcomes. Epi Info (Version 3.5.2, 2010, Centers for Disease Control and Prevention, Atlanta, GA.) was used for data entry and all data were double-entered to minimize errors. Means, medians, standard deviations (SD) and ranges were used to examine and describe the distribution of the data, and variables that were not normally distributed were log transformed. Baseline demographic and clinical characteristics were compared using Student’s t and Wilcoxon rank sum tests for continuous variables and Chi-square and Fisher’s exact test for categorical variables. Blood glucose values were transposed and examined longitudinally to depict the average blood glucose on each hospital day (n=2189 observations). Kaplan-Meier analyses and Cox proportional hazard modeling were used to estimate survival. All statistical tests were completed using SAS (Version 9.2, 2008, SAS Institute Inc., Cary, NC). A p value of ≤ 0.05 was considered statistically significant.

RESULTS

Clinical characteristics are described in Table 1 (n=112). In general, patients were 56.9 (± 8.0) years of age and predominantly Non-Hispanic black (44%). The majority of patients reported a history of cardiovascular disease (54%) and diabetes was prevalent in 21% (n=24) of participants, with 13% (n=14) using oral hypoglycemic agents and 6% (n=7) using insulin prior to admission. Blood glucose was 6.4 ± 2.1 mmol/L and BMI was 29.3 (± 6.9) at admission, reflecting an obesity prevalence of 42% (BMI≥30) using international cut-

points[15]. The average admission performance scale score was 92 (range 75-95), and nearly all patients were conditioned with melphalan chemotherapy (200 mg/m^2) and dexamethasone (40 mg). All patients had peripheral blood as the stem cell source and the number of CD34+ cells transplanted did not differ by group. Overall, no significant differences were noted between PN and non-PN recipients at baseline, supporting the general comparability of patients prior to PN initiation. PN initiation was at the discretion of the attending physicians; however, each transplant institution had registered dietitians and pharmacists to assist with PN management. On average, PN provided 1709 kcals and 82 grams of protein (25 kilocalories/kg and 1.2 grams protein/kg) and lipid emulsions were provided as a routine component of PN.

As depicted in Figure 1, blood glucose levels were elevated during the first few days of transplant hospitalization and then following the time of PN administration. Only 3 individuals received steroids outside of the conditioning chemotherapy regimen; thus, their influence on overall glycemic control was minimal. During hospitalization, insulin was administered to 27% (n=30) of all patients. No differences were detected between PN vs. non-PN recipients [32% (n=16) vs. 23% (n=14), respectively, p =0.26]. Of these, 63% (n=19) reported a history of DM.

Table 2 and Table 3 depict the relevant clinical characteristics and secondary outcomes between feeding strata and the application of the “before” and “after” methodology for specific variables, respectively. Significant declines in oral intake were observed “before” PN initiation in PN recipients compared to non-PN patients; however, no differences in mucositis and emesis were noted during this interval. The incidence of mucositis was significantly greater “after” in PN vs. non-PN patients ($p<0.001$), but no differences were detected for oral intake or emesis “after.” The incidence of neutropenic fever was significantly higher in PN patients vs. non-PN patients ($p<0.001$), occurring on transplant day 6 for PN patients and transplant day 7 for non-PN patients. No specific organisms were identified during neutropenic fever and no differences were found for total infection or infection “before” or “after” between groups. Significant delays in WBC ($p=0.05$) and platelet engraftment ($p=0.009$) were observed, despite the similar percentage of patients with platelets $<20 \times 10^3/\mu L$ in the PN vs. non-PN groups ($p=0.40$). Although the number of RBC and platelet transfusions were not different “before” between PN groups, there were significantly greater transfusion requirements for RBC ($p=0.0014$) and platelets ($p=0.001$) “after” between groups, respectively. PN recipients also experienced significantly longer hospital stays ($p<0.001$) than non-PN recipients.

The 5-year mortality for this cohort was 40% (n=45/112) with 42% mortality (n=26/62) in those who received PN and 38% mortality (n=19/50) in non-PN recipients. Kaplan-Meier analyses ($p=0.42$) (Figure 2) and Cox PH models revealed no differences in 5 year survival rates between PN and non-PN recipients, after controlling for age, race, gender and BMI (HR 0.85, 95% CI 0.47-1.56).

Discussion

While PN administration has proven to be lifesaving in patients with permanent gastrointestinal failure, its role in those with temporary gastrointestinal failure remains elusive. The present study demonstrated that short-term PN administration was associated with unfavorable effects on blood glucose control, delays in WBC and platelet engraftment, a greater need for blood product support and no apparent survival advantage. Three separate working groups have convened to publish evidence-based clinical guidelines to help streamline PN therapy during SCT[16-18]. These committees recommend that patients who experience sustained periods of suboptimal oral intake, severe mucositis, intractable vomiting or 'malnourished patients' be considered PN candidates. Significant decreases in oral intake were observed in the PN patients compared to the non-PN patients; however, no differences in mucositis or emesis patterns were noted. A recent study by Habschmidt et al, surveyed Registered Dietitians practicing in the area of SCT. Survey participants reported that oral intake was the predominant form of medical nutrition therapy (MNT) utilized in their SCT practice and that PN was utilized 16-31% of the time[19]. As not all clinical practice can be reduced to algorithms and treatment scenarios, variations from published guidelines in PN use are expected. Forty-five% of patients in our study received PN, signifying a relatively high PN administration rate and the considerable possibility that PN was not warranted in a great deal of these patients. Due to the retrospective study design, data on the nutritional status of these individuals was not ascertainable to further assess compliance with current guidelines. Iverson et al[20] reported transient decreases in the nutritional status of myeloma patients using anthropometric (eg, BMI) and biomarker data (eg, serum albumin, serum transferrin, Vitamins D and E), signifying acute fluctuations and perhaps the limitations of these nutritional status measures. More recently, Dupire et al found the Prognostic Inflammatory and Nutritional Index (PINI) was useful for the determining the prognosis of patient with myeloma[21]; however, this tool largely relies on acute phase proteins which are not considered valid nutritional status markers[22]. Because clinical practice lacks a universal tool to decipher malnourished patients from those that are 'normally' nourished, this committee recommendation remains limited. The Patient Generated Subjective Global Assessment (PG-SGA)[23], a cancer-specific malnutrition classification tool adapted from the original SGA[24, 25], has been used to signify nutritional deficits in patients prior to SCT[26]. Utilization of this tool offers numerous possibilities for future research efforts to help in the systematic identification of malnourished patients in support of these working group recommendations.

In January, 2012 the American Diabetes Association (ADA) published their consensus statement on inpatient glycemic control for non-critically ill patients[27]. Since prospective randomized clinical trials in non-critically ill patients remain insufficient, experts relied upon clinical experience and judgment when formulating these guidelines. The most current recommends for the non-critically ill specify premeal blood glucose targets of <7.8 mmol/L with random blood glucose <10.0 mmol/L. Per these recommendations, all patients in the current study were within acceptable blood glucose limits, yet adverse associations were observed. Because patients receiving SCT are not critically ill, nor do they reflect the illness acuity for the average hospital floor patient, these dichotomized blood glucose

recommendations may perhaps fail to recognize this hybrid group of patients who would benefit from more stringent blood glucose criteria. Regardless, our findings are consistent with those of Cetin et al[28] who reported significant delays in platelet engraftment for auto-SCT patients who received greater dextrose loads. We speculate that hyperglycemia disrupts the stem cell environment responsible for providing essential cues for the maintenance, function and ultimate fate of the stem cell. Using mouse models of diabetes, Orlandi et al[29] demonstrated that bone marrow cells from diabetic mice receiving sub-lethal doses of radiation exhibited significantly lower engraftment and repopulation capacity compared to bone marrow cells from healthy mice. Although extrapolating this in vivo animal model work to humans has limitations, it supports the biological plausibility of the altered cellular functions observed here.

No differences in survival rates between feeding groups were detected. These analyses were largely motivated by an earlier investigation which indicated that prophylactic PN positively influenced 3-year survival for patients treated with bone marrow transplantation[30]. Our results are difficult to directly compare to this work as a variety of diagnoses were included and transplant practices have changed immensely since the time of the Weisdorf et al publication. However, consistent with our findings, subgroup analyses restricted to autologous patients revealed no differences in survival outcomes[30]. Sonabend et al conducted a retrospective cohort in children diagnosed with acute lymphocytic leukemia (ALL) and treated with L-asparaginase and high-dose corticosteroids; both, of which, are associated with hyperglycemia. Sustained blood glucose levels >11.1 mmol/L during induction therapy were associated with decreased relapse-free survival (RFS) and overall (OS) at 5 years when compared to euglycemic participants (blood glucose <7.8 mmol/L) [13]. Recently, Lee and Longo described how fasting induces important cellular changes that are ultimately protective for the host and harmful to tumor cells [31]. The precise mechanisms are not comprehensively understood, yet current models support reductions in glucose are associated with concomitant decreases in insulin-like growth factor I (IGF-I), and down regulations of Akt, mTOR and Ras. These alterations withdraw cellular efforts from growth/reproduction and reinvest it in maintenance and repair, thereby increasing cellular protection. Using mammalian cancer cell lines, Lee et al subsequently demonstrated that fasting reduced cancer cell proliferation, increased cancer cell death, delayed progression of different tumors and increased effectiveness of anti-neoplastic drug therapies[32]. Feeding is speculated to reduce the evolutionary mechanisms essential for cellular maintenance and survival (ie, autophagy)[31]. Consequently, non-cancerous cells become prone to chemotherapy and paradoxically, malignant cells resistant to cytotoxic agents. Thus, feeding can, in turn, suppress tumor responsiveness and intensify chemotherapy side- effects. Human trials exploring these hypotheses are underway[33]. We believe that the increased relapse and decreased survival reported previously[12, 13] may be explained by these cellular alterations.

These data provide a unique opportunity to explore the effects of an aggressive nutrition therapy without the ethical dilemmas or financial burden of a clinical trial (ie, withholding PN from a candidate who is deemed eligible, or conversely, providing PN when it is not clinically indicated.) Despite this methodological gain, this study is not without limitations. First, due to the retrospective study design, we were unable to identify the clinical triggers of

PN therapy and therefore, unable to determine if PN patients were fundamentally different. The possibility that PN recipients were sicker cannot be ruled out and until a severity of illness measure becomes available, this will always temper interpretations regarding parenterally fed patients undergoing SCT. Further, as previously mentioned, our study design did not permit the determination of nutritional status to see if compromises were more frequent among PN vs. non-PN patients. If malnutrition were more prevalent among the PN recipients, this may lend itself to a less hospitable bone marrow microenvironment to support engraftment, thus prolonging cytopenias, delaying engraftment and increasing the need for transfusional support. Second, our 5-year mortality data were considerably lower than national averages, limiting the generalizability of these findings and providing the plausibility that this was a 'healthier' SCT cohort. Without reliable follow up treatment data it is difficult to discern if the approval of novel agents in the subsequent years is responsible for these superior mortality findings. Third, although our sample size was comparable to other investigations, post-hoc analyses revealed that we would need ~200 patients to determine the effects of short-term hyperglycemia on mortality. Finally, because this was not a clinical trial with random allocation of known and unknown confounders on the 'exposure-outcome' relationship, causality cannot be conferred. These data simply provide associative relationships.

Conclusions

The study demonstrated that myeloma patients undergoing initial auto-SCT experience elevations in blood glucose during the first few days of hospitalization and following PN initiation. Even though clinicians prescribe PN to improve outcomes, this data support that it is associated with significant incident hyperglycemia, delays in both, WBC and platelet engraftment, the need for greater blood product support, and no 5-year survival advantage when compared to those who consumed food *ad libitum*. The molecular advantages of fasting are well supported using model organisms and it may be that providing patients with PN during conditioning chemotherapy may disrupt evolutionary mechanisms fundamentally protective to the host. Moreover, although hyperglycemia was the focal mechanism of this study, it may be that feeding *per se* disrupts critically important pathways for host survival. Currently, the American Cancer Society encourages increased calorie and protein intake during cancer treatment and recovery[34]; however, the anorexia observed clinically during conditioning chemotherapy in this patient population may be an underappreciated, evolved response that perhaps should not be ignored. To provide scientifically sound evidence for further clinical guideline development, future studies should seek to examine the implications of fasting, as well as the effect of non-invasive individualized medical nutrition therapies on outcomes in this frequent SCT population.

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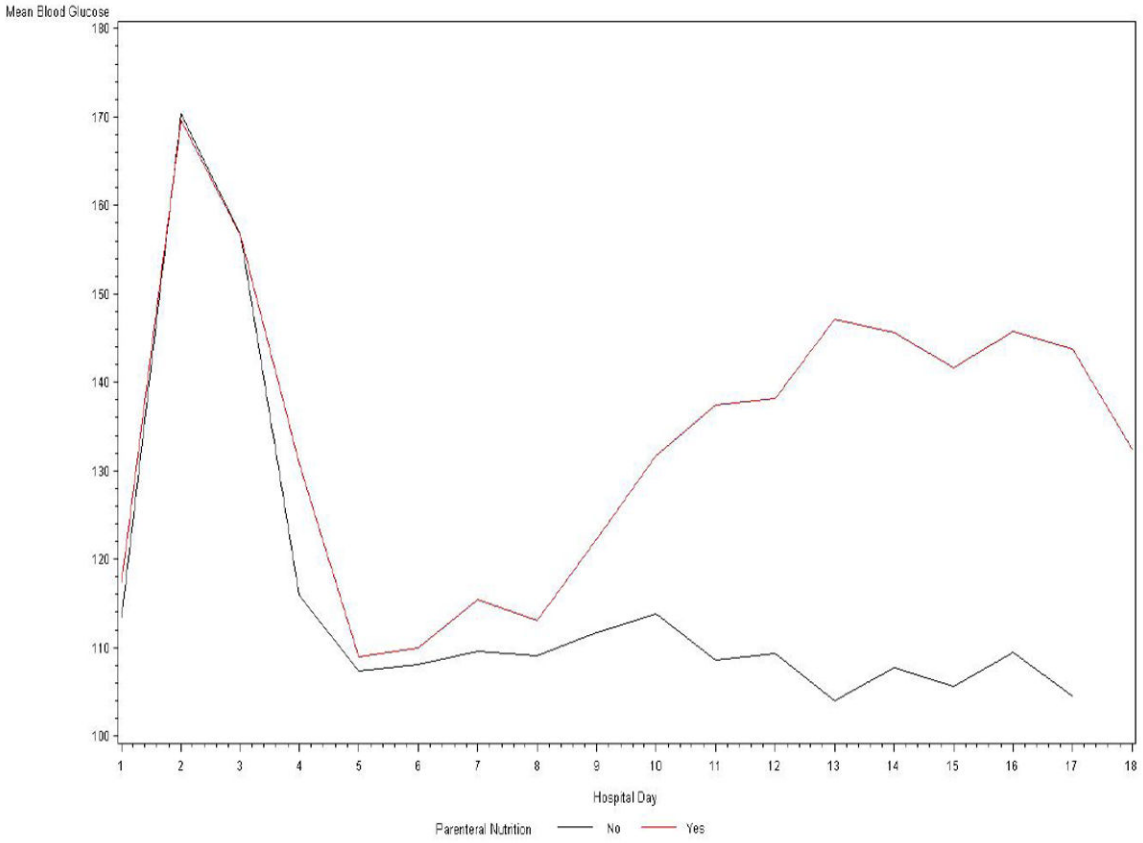

Figure 1.
Longitudinal blood glucose levels (n=2189) reflecting average levels for each hospital day stratified by PN (N = 112).

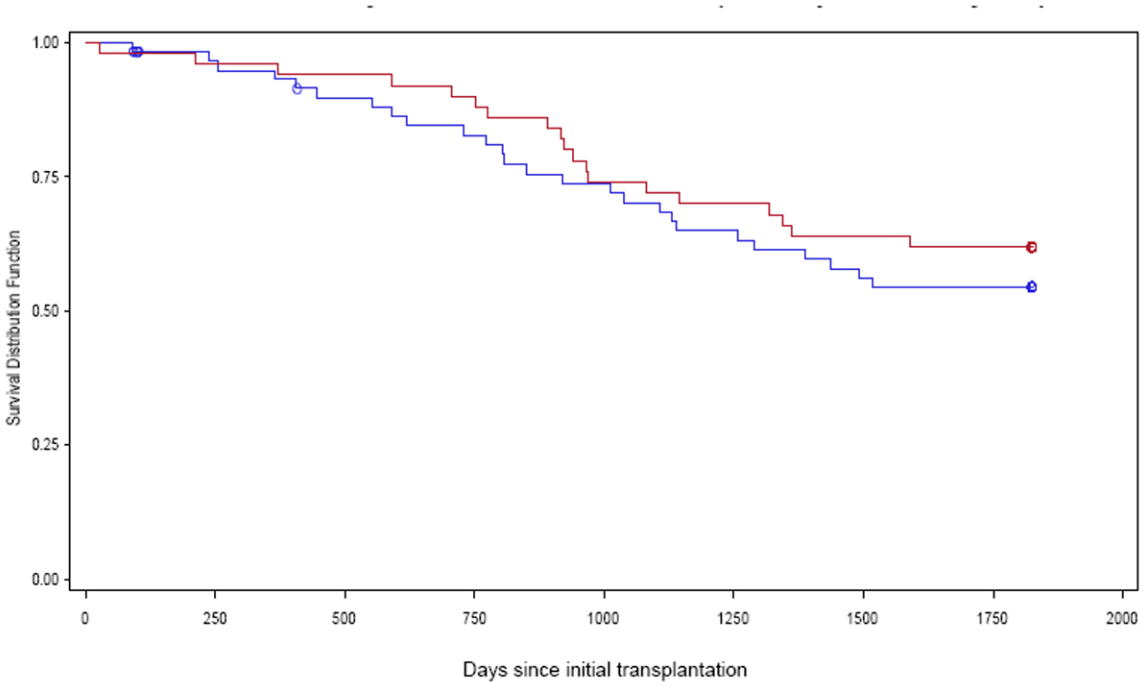

Figure 2.

Kaplan-Meier curves reflecting 5 year survival stratified by parenteral nutrition (PN)

PN recipients = red line, non-PN recipients = blue line, circles indicated right-censored data

Table 1

Patient demographics and clinical characteristics stratified by parenteral nutrition (PN) exposure[a] (N=112)

	Parenteral Nutrition n=50	No Parenteral Nutrition n=62	P value
Sex			0.97
Male	24 (48%)	30 (48%)	
Female	26 (52%)	32 (52%)	
Age (years)	57.9 ± 7.7	55.9 ± 8.2	0.20
Race			0.21
Non-Hispanic white	21 (42%)	22 (35%)	
Non-Hispanic black	20 (40%)	27 (44%)	
Hispanic	5 (10%)	12 (19%)	
Other	4 (8%)	1 (1%)	
Body mass index[b]	28.2 ± 5.9	30.4 ± 7.9	0.12
Obese	18 (16%)	30 (27%)	0.19
History of Cardiovascular disease	27 (54%)	34 (55%)	0.93
Diabetes mellitus	7 (14%)	17 (27%)	0.09
Admission glucose	117 ± 44	113 ± 32	0.61
Admission Karnofsky Score	92	91	0.87
Conditioning Chemotherapy			
Melphalan	50 (100%)	61 (98%)	0.99
Other	0 (0%)	1 (2%)	
CD34+ cells transplanted	7.37 ± 5.6	6.6 ± 3.3	0.66
Received insulin	16 (32%)	14 (22%)	0.26
Alive at Discharge	49 (98%)	62 (100%)	0.45

[a] Data are n (%) or means ± standard deviation (SD.)

[b] Obese was defined as a body mass index (BMI) ≥30 kg/m^2.

Table 2

Stem cell transplant characteristics and secondary outcomes stratified by parenteral nutrition (PN)[a]

	PN (n=50)	Non-PN (n=62)	P value
Neutropenic fever	47 (94%)	42 (68%)	<0.001
Total Infections	0.69 ± .85	0.56 ± .76	0.48
White blood cell engraftment day [b] (range)	12.2 ± 1.8 (9-21 days)	11.5 ± 2.0 (8-16 days)	0.05
Platelet Engraftment day [c] (range)	17.4 ± 5.5 (11-34 days)	12.9 ± 2.9 (10-20 days)	0.009
Total transfusions	8.1 ± 4.8	4.7 ± 3.4	<0.001
Length of hospitalization (days)	22.5 ± 6.7	17.9 ± 3.1	<0.001
Alive 5 years post-SCT	31 (62%)	36 (58%)	0.42

[a] Plus-minus values are means ± standard deviation.

[b] WBC engraftment time was defined as the number of days between transplant day 0 and the first day of 3 consecutive days that the ANC was > 0.5×10^9/L.

[c] Platelet engraftment time was defined as the post-transplant day when platelets were > 50×10^9/L and platelet independent for at least 7 days. The majority were not platelet independent prior to discharge in either feeding group.

Table 3

Incidence and temporality of clinical characteristics and clinical occurrences stratified by parenteral nutrition administration[a]

	Parenteral Nutrition (n=50)		No Parenteral Nutrition (n=62)		P value	
	Before[b]	After[c]	Before	After	Before	After
Oral intake[d]	75 ± 24	73 ± 30	97 ± .06	84 ± .10	<0.001	0.60
Emesis[d]	18 ± 19	15 ± 16	10 ± 14	8 ± 12	0.60	0.06
Mucositis[d]	10 ± 14	44 ± 36	7 ± 13	17 ± 28	0.22	<0.001
Hyperglycemia (≥7.0 mmol/L)	30 ± 25	56 ± 34	29 ± 22	10 ± 16	0.99	<0.001
Infections	0.27 ± .57	0.38 ± 0.67	0.24 ± .47	0.24 ± 0.27	0.93	0.37
RBC Transfusions	1.06 ± 1.15	1.98 ± 2.20	1.19 ± 1.34	0.87 ± 1.09	0.68	0.0014
Platelet Transfusions	0.32 ± 0.71	3.14 ± 4.50	0.42 ± 0.82	1.63 ± 2.67	0.48	0.001

[a] Data are presented as means ± standard deviation.

[b] Before signifies the existence of the event in the time preceding PN administration or hospital days 1-9 for non-PN recipients.

[c] After signifies the existence of the event in the time following PN administration or hospital days 10-19 for non-PN recipients.

[d] Percent of hospital days (± standard deviation) with oral intake ≥500 mL per day or the occurrence of emesis (yes/no) or mucositis (yes/no).