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CLINICAL RESEARCH

A liberalized diet does not improve caloric intake during neutropenia in patients undergoing hematopoietic stem cell transplants: A prospective randomized controlled trial

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Abstract

Background: The neutropenic diet has been a long-standing approach to preventing infection in patients with hematopoietic stem cell transplants (HSCTs), although data on its efficacy are inconclusive and its restrictive nature might contribute to harm by reducing dietary intake in this patient population who typically experiences poor oral intake. The aim was to determine if a liberalized diet (LD), in comparison with a neutropenic hospital diet (ND), would improve energy intake and lessen weight loss during neutropenia in patients with HSCTs.

Methods: A randomized controlled trial was conducted in a single-center HSCT/hematologic malignancy unit. The diet interventions were initiated when absolute neutrophil counts dropped to <500 cells/mm^3; oral dietary intake was assessed during neutropenia until neutrophil recovery, which averaged 9.5 days.

Results: Meal intake compliance (consuming at least 50% of meals/day) was not different between groups (LD, 47%; ND, 43%; $P = 0.66$). Of the 191 patients assessed (LD, $n = 92$; ND, $n = 99$), mean (SD) energy, 678 (349) vs 724 (393) kcal/d ($P = 0.46$), and protein, 30.3 (18.5) vs 30.4 (18.1) g/day ($P = 0.89$) did not differ between groups nor did weight change, 0.3 (2.5) vs 1.2 (4.1) kg ($P = 0.22$) during neutropenia. None vs higher than or equal to grade 1 mucositis, allogeneic vs autologous stem cell transplantation, and fewer days on intervention favored higher energy and protein intakes.

Conclusion: Energy intake during neutropenia did not improve with a LD encouraging fresh fruits and vegetables. Thus, alternative approaches to improving dietary intake, such as energy-dense and nutrient-dense foods with

sensory characteristics acceptable to patients experiencing significant mucositis, require exploration.

KEYWORDS
adult, hematopoietic/stem cell transplant, life cycle, neutropenic diet, oncology, research and diseases, weight loss

INTRODUCTION

The "low bacterial" diet dates back >50 years,[1,2] evolving into the neutropenic diet prescribed to protect chemotherapy patients from potentially life-threatening infections during neutropenia.[3] Specifically, the neutropenic diet may be prescribed for acute myeloid leukemia/myelodysplastic syndromes, acute lymphoblastic leukemia, and autologous and allogeneic hematopoietic stem cell transplant (HSCT). It is generally initiated when absolute neutrophil counts (ANC) are low (<500 cells/mm^3) or at the start of a cytotoxic chemotherapy regimen that is anticipated to result in neutropenia and is continued until neutrophil recovery. The premise is that most cytotoxic chemotherapy regimens cause gastrointestinal mucosal injury as well as neutropenia.[4] Enteric colonizing bacteria, as well as ingested food-borne bacteria, can more easily invade through the damaged intestinal mucosa into the normally sterile tissue, eventually entering the portal circulation. With a paucity or absence of circulating neutrophils as a second line of defense, severe tissue infection or systemic bacteremia may result.[4] The diet is given to reduce the ingestion of pathogenic food-borne microorganisms until neutrophil recovery and concomitant healing of the mucosal injury.

The neutropenic diet incorporates low-microbial diet recommendations, which restrict high-risk foods such as raw or rare-cooked meat, fish, poultry, undercooked eggs, raw nuts, and unpasteurized dairy products.[5] Fresh fruits, vegetables, and yogurt with live cultures are typically also excluded.[3] For ambulatory outpatients, there are commonly additional restrictions to avoid deli meats and soft cheeses, salad bars, and foods from street vendors.[3] Most neutropenic diet restrictions for inpatients are in accordance with the stringent federal[6] and state food safety guidelines adhered to by US hospital food services, that is, high-risk foods such as rare meat, undercooked eggs, and unpasteurized dairy products are not served. However, restricting fresh fruits and vegetables has been questioned[7,8] because this exclusion was generally not included in national and international expert panel recommendations.[9,10] From a food safety perspective, cooked and canned fruits and vegetables are safest; however, the relative risk of food-borne illness from the microbial contamination of fresh fruits and vegetables is low,[11] particularly in hospital food services departments with reliably sourced foods and adherence to stringent food-safe handling and preparation. Hospital-acquired food-borne illness in the United States is exceedingly rare,[12,13] considering the estimated 40 million food-borne illnesses resulting in 3000 deaths annually.[14]

Considering the principle of nonmaleficence, the balance of benefit vs harm of a neutropenic diet prescription requires consideration. In 2016, a Cochrane review of the efficacy of the neutropenic diet concluded that there was "no evidence of effect" for reducing infection rates because of the many methodological limitations of the included studies.[15] However, the authors emphasized that this conclusion was not meant to suggest "evidence of no effect," indicating a need for well-designed randomized controlled trials to determine the efficacy of the neutropenic diet. Subsequent systematic reviews with meta-analysis conclude that there is no conclusive evidence to support neutropenic diet food restrictions.[16,17] However, reviews have typically excluded HSCT patients.[15,17] The European Society for Clinical Nutrition and Metabolism (ESPEN) consensus guideline on hospital nutrition states that "Neutropenic diets...shall not be used...in neutropenic patients with cancer including hematopoietic cell transplant patients."[18] Most recently, Radhakrishnan et al reported that a neutropenic diet was ineffective in reducing infections or mortality in patients with acute leukemia.[19] Similarly, Stella et al concluded that a nonrestrictive diet was not inferior to a "protective" neutropenic diet in HSCT patients with respect to the incidence of infectious toxicity, although documented infections were not assessed.[20] However, in a European survey, 86% of responding institutions continue to provide a low-microbial diet during neutropenia for allogeneic HSCT patients,[21] and, in recent years, 35% of top-ranked US cancer centers promoted the neutropenic diet on their websites.[22]

Furthermore, a standard hospital diet has been shown to be safe for neutropenic patients, demonstrating fewer diarrhea events, nausea, and weight loss than for patients prescribed a neutropenic diet.[23] Additionally, dietary restrictions may be harmful from the patient's perspective of diet palatability and the potential negative

impact on dietary intake. Given the questionable efficacy of the neutropenic diet in preventing infection, the risks associated with unnecessary dietary restrictions for HSCT patients require investigation, particularly given their notably poor food intake during neutropenia attributed to treatment-related mucositis, nausea, vomiting, and diarrhea.[24] Malnutrition in the HSCT population is negatively associated with survival and relapse risk.[25] Because these patients are often malnourished on admission,[26] further weight loss because of low energy intake adversely affects clinical outcomes.[27,28] Limited systematic research has been undertaken to examine the dietary intake of HSCT patients during neutropenia[29]; instead, the focus has typically been on intakes pretransplant and posttransplant.[30,31] However, evidence of declining nutrition status during neutropenia suggests that dietary intake is very poor.[24,27]

Patients undergoing chemotherapy, radiotherapy, and HSCT have reported preferences for fruits, vegetables, juices, and soups, because these foods were associated with improving gastrointestinal symptoms.[32] Oral food intake is recommended during neutropenia,[33] and restricting fresh fruits and vegetables may negatively impact food intake. Conversely, a diet including these fresh foods may enhance overall food intake and diet quality. Given the risks associated with weight loss in patients with HSCTs, the primary aim of this analysis was to determine if a liberalized diet, encouraging fresh fruits and vegetables, promotes higher energy intake compared with a neutropenic diet prescription in autologous and allogeneic HSCT patients. It was hypothesized that HSCT recipients consuming a liberalized diet would consume more energy and exhibit less weight loss during neutropenia than those consuming a more restrictive neutropenic diet. The secondary aims were to assess protein intake and the relationships between mucositis, energy intake, and weight loss.

METHODS

This study is the dietary intake analysis of a randomized, open-label, phase 3 trial testing the noninferiority of a liberalized, food-safe diet inclusive of fresh fruits and vegetables vs a neutropenic diet in patients with prolonged neutropenia because of HSCT or treatment for acute myeloid leukemia, acute lymphoblastic leukemia, or myelodysplastic syndrome. The present analysis examines energy and protein intake, mucositis, and weight change. Major infection rate was the primary end point of the clinical trial, and quality of life and survival outcomes were key secondary end points (data to be reported in upcoming publications). The present analysis examines energy and protein intake, and body weight between groups. The Institutional Review Board of the University of Florida (IRB201700581) approved the study, registered at clincaltrials.gov (NCT03016130) on January 10, 2017. Procedures complied with the Declaration of Helsinki. All participants provided written informed consent.

Study participants

Participants (≥18 years of age) with either (1) an underlying diagnosis of acute myeloid leukemia/acute lymphoblastic leukemia/myelodysplastic syndrome receiving induction or reinduction chemotherapy; (2) a diagnosis of acute lymphoblastic leukemia with an expected duration of neutropenia of ≥7 days; or (3) any participant undergoing allogeneic or autologous HSCT for any indication were recruited from a single academic HSCT/hematologic malignancy unit in Florida, United States, between September 2017 and August 2023. However, for this dietary analysis, a subset was used. Only enrolled patients undergoing allogeneic or autologous HSCT were included. Additionally, patients with no reported dietary intake were excluded. Receiving nutrition via an enteral tube or parenteral nutrition at enrollment or being unwilling to eat fresh fruit or vegetables were among the exclusion criteria.

Diet intervention

Patients received one of two diets: liberalized (LD) or standard neutropenic (ND). Randomization was done by a computer algorithm, stratified by the subgroups within the study population, specifically autologous and allogeneic HSCT recipients, for the present analysis. Permuted block randomization with a block size of four within each group was used to randomize the eligible patients to either the LD or ND. The nurses collecting dietary intake data were not blinded to the patient's assigned diet; they observed patient meal trays and were instructed to encourage fresh fruits/vegetables (if on the LD). The dietitians who assessed compliance to each diet arm were not blinded. Statistical analysis was blinded.

The LD included fresh fruits and vegetables, and patients were encouraged to eat at least one serving daily. Fresh vegetables offered on the hospital menu were typically salads, and examples of fresh fruits offered are bananas, pineapple, grapes, and strawberries. Any consumption of fresh fruits and vegetables was considered nonadherence to the neutropenic diet. Both diets followed the FDA-endorsed food safety guidelines.[6] The diet interventions were

initiated on the day when ANC dropped to <500 cells/mm^3 and continued until the ANC was ≥500 cells/mm^3, the patient was discharged from the hospital or the patient was transferred from the HSCT/hematologic malignancy unit, or after 30 days of ANC <500 cells/mm^3; whichever occurred first.

Intake of fresh fruits and vegetables was documented, and fruit and vegetable compliance was determined based on whether the patient adhered to the appropriate dietary intervention based on their randomization. Specifically, adherence to the LD was defined as ≥1 serving per day of fresh fruits and vegetables and, for the neutropenic diet, zero servings of fresh FV (FV compliance). Meal intake compliance was defined as consuming at least 50% of their meals daily; information was entered in the Nursing Flowsheet in Epic.

Additionally, mucositis was assessed by nursing staff using the National Cancer Institute criteria of Grades I to V (highest score reported during neutropenia) and dichotomized as none vs grade I or above.[34]

Outcome measures

Mean daily energy intake, mean daily protein intake, and weight change during neutropenia were the outcome variables assessed. Mean daily energy (kcal/day) and protein intake (g/day) during neutropenia were determined as follows. The oral food intake of HSCT patients was assessed during the period of neutropenia. Registered nurses documented meal consumption in the Calorie Count Analysis flowsheet in the electronic health record software system (Epic Systems Corporation). Meal intake was documented as the percentage of meat, vegetables, sandwiches, cereal, soup, and so forth, consumed by the patient. The specific foods were confirmed via comments in Epic's Calorie Count Analysis flowsheet or by comparing the documented intake with the corresponding meal ticket, accessed through an online MyDining (2.21.0) portal. The energy and protein contents of food provided by the hospital were found in a "Menu Nutrient Analysis Report" provided by the food service department. The nutrient content of food not supplied directly from the hospital, such as foods from family (in most cases, snacks), was obtained from the respective manufacturers' websites. Patients were instructed to record all outside food, and the nurses documented the intake in the flowsheet (eg, two Oreo cookies). Consumption of oral nutrition supplements (eg, Ensure Enlive, ScandiShakes, etc) was also documented in the Calorie Count Analysis flowsheet. Finally, mean daily energy (kcal/day) and protein intake (g/day) were calculated. Weight measurements, with patients wearing personal clothing or a hospital gown, were obtained by hospital staff each morning during neutropenia using a calibrated Scaletronix portable standing scale. Weight change was calculated as the difference in body weight at the resolution of neutropenia from baseline weight at the onset of neutropenia (and the initiation of diet intervention).

Statistical analysis

Distributions of variables, including out-of-range and missing value patterns, were examined using descriptive statistics appropriate for measurement level (eg, mean, standard deviation, and range for continuous variables, frequency, and percent for categorical variables). Tenability of statistical model assumptions was evaluated, and appropriate remedial measures (eg, use of nonparametric methods or robust regression) were applied where required. All analyses were performed using SAS version 9.4.[35] A 5% Type I error rate was used for inferential tests.

The primary nutrition aim was to compare mean energy intake (kcal/day) during neutropenia between randomly assigned liberalized and neutropenic diet treatment groups of autologous and allogeneic HSCT recipients (intent-to-treat). The main effect was diet treatment, liberalized vs neutropenic. The primary outcome, energy (kcal/day), and protein (g/day) intakes were directly compared between diet treatment groups of HSCT patients using nonparametric Wilcoxon rank sum tests.[36]

As additional variables may have affected response to diet treatment, multiple regression models containing selected covariates, namely conditioning type (myeloablative/nonmyeloablative or reduced intensity), transplant type (allogenic/autologous), days on intervention, presence of mucositis, and sex (male/female), along with the covariate-by-diet group interactions, were explored as secondary aims. Covariate-by-diet group interactions with $P \geq 0.05$ were dropped from the multiple regression models. For interactions with $P < 0.05$, simple main effects analyses were performed to identify the form of the interaction. Because of outliers in the data, robust multiple regression models, using SAS PROC ROBUSTREG, were evaluated,[37] applying the MM estimation technique, which uses a least trimmed squares estimate of the regression weight parameter as a starting value, estimates a scale parameter using Tukey bisquare function, and then uses M estimation to produce the final robust regression weight estimate.[38]

RESULTS

The study flow diagram is shown in Figure 1. Of the 214 participants who completed the trial, dietary intake data was available on 191 HSCT patients who underwent

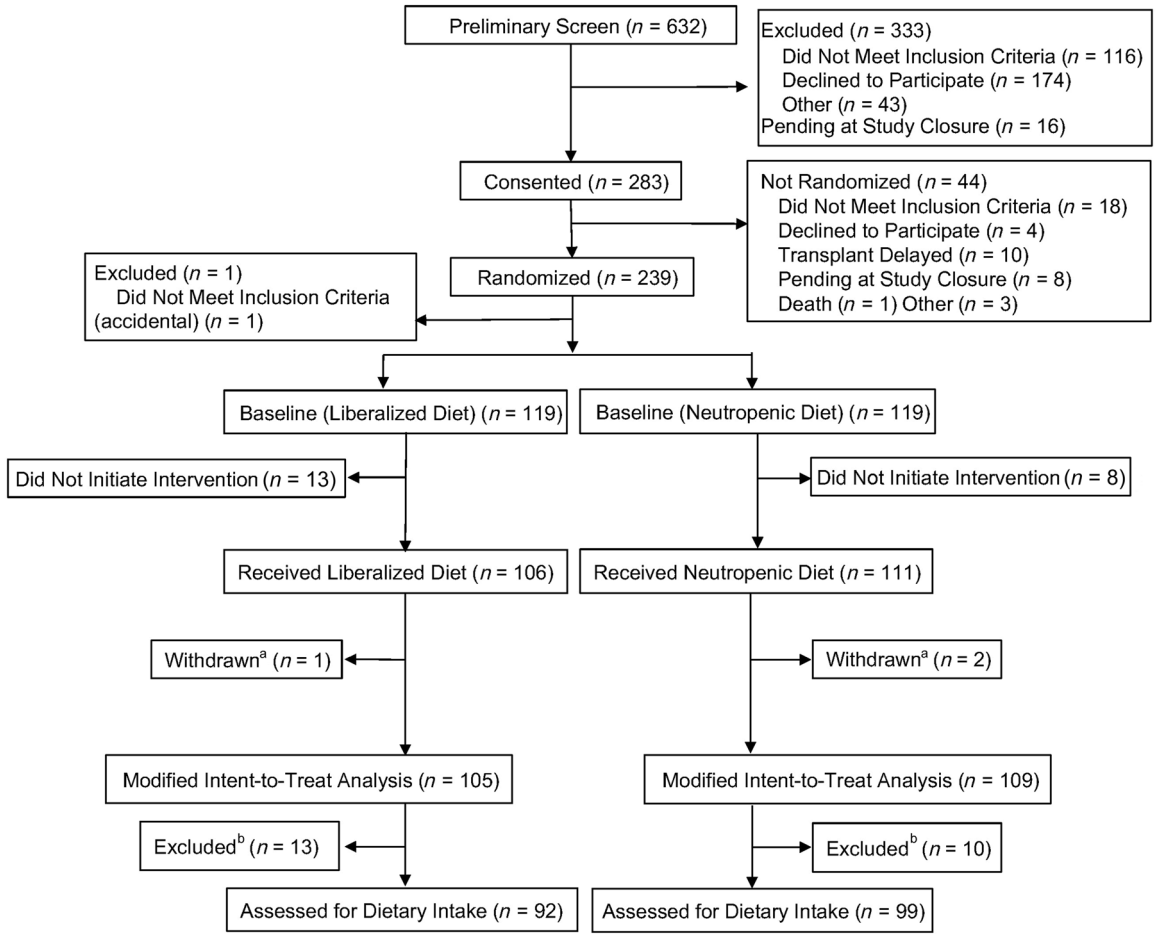

FIGURE 1 Study flow diagram. [a]Withdrawn because of infection before initiating interventional diet but identified after initiation. [b]Excluded from analysis because of not undergoing allogeneic or autologous hematopoietic stem cell transplant (HSCT) or no dietary intake data.

HSCT. Participants ranged from 23 to 79 years of age, with a mean of 58 ± 12.9 years, and most (76%) received an autologous HSCT (Table 1). Demographics, body weight, and transplant characteristics of the study population are shown in Table 1. Calorie count documentation was completed for 77% of patient intervention days. All patients randomized to the neutropenic diet were compliant with the prescribed fresh FV restriction, and 52% of patients randomized to the LD were compliant with FV intake. The distributions of intake compliance, defined as consuming at least 50% of each meal, between diet groups were similar (Table 1). Mucositis (none vs Grade I and above) was similar between groups, as was the distribution of severity (Table 1). Employing a Wilcoxon test, the intent-to-treat direct comparison between groups confirmed that mean energy intake and protein consumption (Table 2) were similar between diet groups.

A robust general linear model analysis was employed to compare adjusted group means by including the covariates of conditioning regimen, transplant type, days on intervention, mucositis, and sex. Patients experiencing no mucositis had higher mean energy (Table 3) and protein (Table 4) intakes compared with those with grade I and above. Women consumed less energy (Table 3) and protein (Table 4) than men. Additional analysis was conducted to assess sex differences in mucositis, given that this may, in part, provide an explanation for the sex difference in energy and protein. Women had higher odds for mucositis than men (odds ratio [OR] 1.85; 95% CI: 1.04–3.31; $P = 0.04$); 62.6% of women had mucositis vs 47.5% of men. For mucositis severity (using Wilcoxon exact), women had higher values than men, 1.14 (SD 1.15; median: 1.00) and 0.84 (SD 1.06; median: 0; $P = 0.046$), respectively. Allogeneic transplant patients exhibited higher mean energy and protein intakes after controlling for the other variables in the model (Tables 3 and 4, respectively). Days on intervention demonstrated an independent inverse association with mean energy intake (Table 3) and mean protein intake (Table 4);

patients with longer days on intervention tended to have lower values on those outcomes after controlling for other model variables. Associations between weight change with diet type, conditioning regimen, transplant type, days on intervention, mucositis, and sex were not supported (Table 5).

Weight change and percent body weight change were similar between the two diet groups (Table 2). The

TABLE 1 Descriptive characteristics and intervention compliance of hematopoietic stem cell transplant patients.

	Combined Groups ($n = 191$)	Liberalized ($n = 92$)	Neutropenic ($n = 99$)	*P*
Age at transplant, mean (SD) range	58.0 (12.9) 23–79	58.6 (13.3) 23–79	57.6 (12.6) 25–78	0.47[a]
Days on intervention, mean (SD) range	9.5 (4.4) 3–28	9.8 (4.9) 3–28	9.3 (3.9) 5–28	0.48[a]
Sex, *n* (%)				0.03[b]
Male	100 (52)	56 (61)	44 (44)	—
Female	91 (48)	36 (39)	55 (56)	—
Initiation body weight, mean (SD), kg	89.6 (22.2)	88.0 (20.2)	91.1 (23.9)	0.29[a]
Transplant type, *n* (%)				0.50[b]
Autologous	145 (76)	72 (78)	73 (74)	—
Allogeneic	46 (24)	20 (22)	26 (26)	—
Transplant conditioning, *n* (%)				0.26[b]
Myeloablative	138(72)	70 (76)	68 (69)	—
Reduced intensity/nonmyeloablative	53 (28)	22 (24)	31 (31)	—
Primary disease, *n* (%)				0.89[b]
MM	114 (60)	57 (62)	57 (58)	—
Lymphoma	29 (15)	14 (15)	15 (15)	—
AML	16 (8)	7 (8)	9 (9)	—
ALL	11 (6)	5 (5)	6 (6)	—
MDS	9 (5)	5 (5)	4 (4)	—
ALL-B	2 (1)	1 (1)	1 (1)	—
CMML	2 (1)	0 (0)	2 (2)	—
Amyloidosis	1 (0.5)	0 (0)	1 (1)	—
Aplastic Anemia	1 (0.5)	1 (1)	0 (0)	—
CML	1 (0.5)	0 (0)	1 (1)	—
HD	1 (0.5)	0 (0)	1 (1)	—
MDS/MPN	1 (0.5)	1 (1)	0 (0)	—
NHL	1 (0.5)	1 (1)	0 (0)	—
Other	2 (1)	0 (0)	2 (2)	—
Meal intake compliance, *n* (%)				0.66[b]
Yes	85 (45)	43 (47)	42 (43)	—
No	103 (55)	48 (53)	55 (57)	—
Fruit/vegetable compliance, *n* (%)				<0.0001[b]
Yes	144 (77)	47 (52)	97 (100)	—
No	44 (23)	44 (48)	0 (0)	—
Mucositis, *n* (%)				0.47[b]
Yes	104 (55)	53 (58)	51 (52)	—

(Continues)

TABLE 1 (Continued)

	Combined Groups ($n = 191$)	Liberalized ($n = 92$)	Neutropenic ($n = 99$)	*P*
No	86 (45)	39 (42)	47 (48)	—
Mucositis severity, mean (SD) range	0.98 (1.1) 0–4	0.97 (1.0) 0–4	1.0 (1.2) 0–4	0.83[a]

Abbreviations: ALL, acute lymphoblastic leukemia; ALL-B, acute lymphoblastic leukemia, B-cell type; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; CMML, chronic myelomonocytic leukemia; HD, Hodgkin lymphoma (Hodgkin's disease); MDS, myelodysplastic syndromes; MDS/MPN, myelodysplastic/myeloproliferative neoplasms; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes.

[a]Wilcoxon test.

[b]Exact *P* value for likelihood ratio χ^2.

TABLE 2 Dietary intake and weight change during neutropenia[a] of hematopoietic stem cell transplant patients.

Mean (SD) range	Combined groups	Liberalized ($n = 92$)	Neutropenic[a] ($n = 99$)	*P*
Energy intake, kcal	702 (372) 47–2384	678 (349) 47–1573	724 (393) 47–2384	0.46
Energy intake, kcal/kg	8.2 (4.6) 0.47–24.4	8.0 (4.2) 0.64–16.9	8.4 (4.9) 0.47–24.4	0.71
Protein intake, g	30.4 (18.2) 0–94	30.3 (18.5) 0–73	30.4 (18.1) 1–94	0.89
Protein intake, g/kg	0.35 (0.21) 0.0–0.96	0.35 (0.22) 0.0–0.87	0.35 (0.21) 0.01–0.96	0.97
Weight change, kg	0.8 (3.4) −5.1–25.3	0.3 (2.5) −5.1–9.1	1.2 (4.1) −4.9–25.3	0.22
Weight change, %	0.9 (4.0) −6.3–30.2	0.4 (2.8) −5.7–7.4	1.4 (4.8) −6.3–30.2	0.25

[a]Mean days on neutropenia was 9.5 (4.4).

TABLE 3 Final robust general linear model[39] results for mean energy intake (kcal) of hematopoietic stem cell transplant patients.

Parameter	WLS estimate (standard error)	95% CI	χ^2 (*df*)	*P*
Intercept	720.6 (95.9)	532 to 908		
Diet LD[a]	−28.0 (50.5)	−127 to 70.9	0.31 (1)	0.58
Myeloablative conditioning[b]	116.9 (70.8)	−21.8 to 255.6	2.7 (1)	0.10
Allogenic transplant[c]	256.7 (94.7)	80.1 to 451.3	7.9 (1)	0.005
Days on intervention	−17.6 (7.9)	−33.1 to −2.1	4.9 (1)	0.03
No mucositis[d]	160.6 (50.4)	61.9 to 259.4	10.2 (1)	0.001
Sex, female[e]	−145.4 (51.3)	−246.0 to −44.8	8.02 (1)	0.005

Abbreviations: LD, liberalized diet; WLS, weighted least squares.

[a]Neutropenic diet is the reference group.

[b]Nonmyeloablative/reduced intensity is the reference group.

[c]Autologous is the reference group.

[d]Mucositis is the reference group.

[e]Male sex is the reference group.

intent-to-treat comparison using the robust general linear model did not support a difference in percent weight change between diet groups after controlling for the selected covariates (Table 5). Neither mucositis nor sex were statistically significant covariates independently associated with change in weight.

DISCUSSION

Compelling evidence suggests that malnutrition contributes to negative outcomes in the HSCT patient population, and weight loss during transplant exacerbates risk for adverse outcomes, including mortality.[25,26,28,40,41] This study

TABLE 4 Final robust general linear model results for mean protein intake (g) of hematopoietic stem cell transplant patients.

Parameter	WLS estimate (standard error)	95% CI	χ^2 (DF)	*P*
Intercept	29.9 (4.8)	20.5 to 39.4		
Diet LD[a]	0.86 (2.5)	−4.1 to 5.8	0.12 (1)	0.73
Myeloablative conditioning[b]	5.1 (3.5)	−1.9 to 12.1	2.1 (1)	0.15
Allogenic transplant[c]	14.5 (4.8)	5.2 to 23.8	9.3 (1)	0.002
Days on intervention	−0.86 (0.40)	−1.6 to −0.08	4.72 (1)	0.03
No mucositis[d]	8.3 (2.5)	3.4 to 13.3	10.8 (1)	0.001
Female sex[e]	−6.7 (2.6)	−11.7 to −1.6	6.7 (1)	0.009

Abbreviations: LD, liberalized diet; WLS, weighted least squares.

[a]Neutropenic diet is the reference group.

[b]Non-myeloablative/reduced intensity is the reference group.

[c]Autologous is the reference group.

[d]Mucositis is the reference group.

[e]Male sex is the reference group.

TABLE 5 Final robust general linear model results for percent weight change.

Parameter	WLS estimate (STD error)	95% CI	χ^2 (DF)	*P*
Intercept	1.3 (0.87)	−0.39 to 3.02		
Diet LD[a]	−0.23 (0.45)	−1.12 to 0.66	0.26 (1)	0.61
Myeloablative conditioning[b]	−0.04 (0.64)	−1.3 to 1.2	0.00 (1)	0.95
Allogenic transplant[c]	0.10 (0.86)	−1.6 to 1.8	0.01 (1)	0.91
Intervention days	−0.09 (0.07)	−0.24 to 0.06	1.42 (1)	0.23
No mucositis[d]	0.34 (0.45)	−0.55 to 1.2	0.57 (1)	0.45
Female sex[e]	0.17 (0.46)	−0.73 to 1.1	0.14 (1)	0.71

Abbreviation: LD, liberalized diet; WLS, weighted least aquares.

[a]Neutropenic diet is the reference group.

[b]Nonmyeloablative/reduced intensity is the reference group.

[c]Autologous is the reference group.

[d]Mucositis is the reference group.

[e]Male sex is the reference group.

provides confirmatory evidence that oral dietary intake during neutropenia is inadequate; patients averaged <10 kcal/kg actual body weight compared with energy recommendations as high as 30 kcal/kg needed to combat catabolism.[42] Previous studies report that most HSCT patients consume much less than reported pretransplant and posttransplant intakes.[43] An older retrospective cross-sectional study showed that the oral diet calorie intake of 36 HSCT patients dropped to 5% of admission energy intake at 1 week posttransplant and rebounded to only 20% at 2 weeks; however, former treatment therapies and aggressive parenteral nutrition support may have contributed to the very low oral intake.[44] Surprisingly, patients receiving allogeneic transplants consumed significantly more energy than those receiving autologous transplants. This finding differs from a retrospective report of dietary intakes of 25 autologous and 10 allogeneic HSCT recipients before transplantation, from transplantation to engraftment, and from engraftment to discharge.[29] The lowest oral diet energy intakes were seen for allogeneic patients from transplantation to engraftment but still exceeded 1000 kcal/day, and autologous recipients consumed 75% of admission intake.[29] The higher energy intake may be due, at least in part, to the use of reduced-intensity conditioning in many allogeneic recipients, with its lower risk of severe mucosal injury. Further investigation is needed to determine why the patients receiving autologous transplants, in particular, had such very low oral intakes.

Protein consumption during neutropenia was inadequate, averaging only 30 g/day. This provided only 0.35 g/kg actual body weight compared with a minimum recommended intake range of 1.4–1.5 g/kg/day and possibly needs as high as 2.0 g/kg/day to preserve lean body mass.[42] In contrast, Garios et al reported much higher protein intakes, ranging from a low of 40 g/day for allogeneic patients to >60 g/day for autologous transplant recipients,[29] whereas So et al reported very low oral intakes of only 2−7 g/day.[44] Clearly, strategies to increase the consumption of protein foods in this patient population are needed.

Unexpectedly, the mean weight change during neutropenia was positive, 0.8 ± 3.4 kg, whereas some patients lost as much as 5 kg, but weight change did not differ between groups. Stella et al reported less body weight in the nonrestrictive diet (−2.7 kg) at 1 month than patients receiving the protective (neutropenic) diet (−3.7 kg), but no differences were found from admittance to discharge.[20] Other researchers have reported weight loss of 3.3%,[45] specifically 5.1% and 3.7% for autologous and allogeneic, respectively.[44] Actual weight loss, defined as loss of lean muscle and fat mass, was likely underestimated in the present study. The substantial weight gains reported in some patients suggest overhydration and edema masking weight loss. Although not documented during this study, given their poor oral intake, many patients would have received intravenous fluids. Additionally, there may have been errors in recording body weight. Future studies should assess body composition preneutropenia and postneutropenia instead of relying on body weight. Specifically, lean body mass should be assessed through objective measures such as bioelectric impedance analysis[46] or ultrasound.[47] Although less sensitive to short-term change, Subjective Global Assessment (eg, PG-SGA), particularly the physical examination, may also inform the loss of lean and fat mass through neutropenia, as has previously been used in the HSCT population.[48]

Unsurprisingly, mucositis was associated with lower dietary intake, given the pain and discomfort of consuming an oral diet. However, mucositis status did not impact body weight status. Indeed, inadequate energy and protein intake because of mucositis would be expected to contribute to a general loss of lean body mass and risk of malnutrition in patients with HSCTs. A previous retrospective study showed a relationship between weight loss and mucositis,[49] but, in that study, researchers were testing a new comprehensive oral mucositis mitigation protocol and excluded patients who did not adhere to the new protocol, thereby potentially biasing the findings. These data, in the context of discrepancies in the reported literature, suggest that oral intake of patients with HSCT may partly depend on transplant center protocol and practices. Thus, there may be an opportunity for optimization.

Offering a more liberalized diet by encouraging fresh fruits and vegetables was not effective in improving the dietary intake in the patients with HSCT. It is possible that the food choices offered, food form (whole vs mechanically processed), and sensory attributes such as flavor and texture, whether liberalized or neutropenic, were generally not acceptable to the HSCT patient population, given their conditioning-related symptoms and personal preferences. Ferreira et al reported a high incidence of hypogeusia during neutropenia, associated with loss of body weight and poor quality of life,[45] and HSCT patients have self-reported serious disruptions in their taste experiences.[50] A limitation of the present study was that no data on patient taste experiences or acceptability of the foods offered were collected. Although mucositis was related to poor food intake overall, it did not explain all the variation in food intake; other factors, such as dysgeusia, anorexia, and decreased salivation, may have contributed to the low intakes, particularly if foods offered were not specifically tailored to the needs and preferences of those patients experiencing such symptoms. Research examining the potential of "food is medicine" approaches to supporting oral intake and diet quality during neutropenia in patients with HSCTs is lacking. Dietary interventions focusing on foods specifically designed to suit patient food preferences and tolerances while easing oral and gastrointestinal complaints require exploration, including qualitative sensory research exploring strategies to address patient taste changes. Further research will strengthen our understanding of the interrelationships among symptoms experienced by HSCT patients, food intake, and wellness.

Given the reported low oral intake, alternate approaches to nutrition support require consideration. HSCT centers demonstrate significant heterogeneity regarding such nutrition support practices.[51] Oral intake is recommended for the patient population with HSCTs, but, if inadequate, enteral is clinically preferred to parenteral[33] but not necessarily by patients.[52] The provision of enteral nutrition is associated with survival, neutrophil recovery, and fewer incidents of acute graft vs host disease (AGVHD),[25] whereas parenteral nutrition has been associated with longer hospital length of stay, specifically in multiple myeloma patients post autologous HSCT.[53] In a systematic review of parenteral vs enteral nutrition in allogeneic HCST during the neutropenic period, the incidence of AGVHD was lower for enteral, but no differences were seen for oral mucositis or overall survival.[54] Traditional enteral formulas or oral nutrition supplements,

including those formulated with ultraprocessed ingredients, may be indicated in the short term to minimize weight loss and avert malnutrition in this patient population.[33] However, an oral diet of fewer processed foods may offer potential benefits for supporting posttransplant wellness and health outcomes in the long-term.[55] Although the patient population with HSCTs may be one of the most challenging patient populations to implement dietary interventions successfully, an adequate oral diet may be instrumental in mitigating posttransplant complications. As HSCT conditioning regimens evolve to less toxic reduced-intensity conditioning regimens, advancements may positively impact patient well-being and the ability to consume an oral diet.

There were limitations of this study. Although an intent-to-treat analysis was completed, only 52% of patients randomized to the LD group consumed any fresh fruits and vegetables, and thus, this level of compliance should be considered when interpreting the results. Future studies are needed to explore why patients experiencing neutropenia specifically may not consume fresh fruits and vegetables when provided. From a nutrition perspective, the most noteworthy limitation of this study was that nutrition status, specifically the prevalence at baseline, incidence, and severity of malnutrition, were not assessed. Future research evaluating dietary interventions to improve oral intake during neutropenia should include an assessment of their impact on malnutrition incidence and severity. To fully inform a globally accepted malnutrition diagnosis, a noninvasive measure of lean body mass, such as bioelectric impedance analysis, should be utilized.[56] Bioelectric impedance analysis, ideally bioimpedance spectroscopy, would also allow for the assessment of hydration status and thus inform the extent to which overhydration is masking weight loss. Regarding the diet intervention, we hypothesized that lifting the restrictions of the neutropenic diet would increase food intake overall and, thus, increase energy and protein intake. However, only fresh fruits and vegetables were directly encouraged, whereas foods such as Greek yogurt (similarly not allowed on the hospital's neutropenic diet), which is higher in calories and provides protein, were not targeted. Promoting a variety of nutrient-dense and energy-dense foods may have influenced the findings. Although significant effort was employed to ensure the accuracy of estimating percentages of individual foods eaten through training of nursing staff, imaging trays preconsumption and postconsumption may have improved the accuracy of the dietary assessment. Although this methodology was considered, it posed an additional food safety risk because of potential delivery delays and the need to remove dish covers for the preconsumption assessment.

In conclusion, patients with HSCTs exhibit very poor oral intake during neutropenia, a time when prevention of malnutrition is paramount to positive outcomes, including survival. However, providing a liberalized diet, including fresh fruits and vegetables, was ineffective in increasing food intake. Future research is needed to explore personalized food and nutrition interventions (targeting texture and taste preferences) to optimize energy and protein intake in the HSCT population during neutropenia. Given the long-term chronic disease risks of HSCT,[57] the potential health effects of increased fruit and vegetable intake and overall diet quality of survivors postneutropenia and discharge require study.

AUTHOR CONTRIBUTIONS

John R. Wingard contributed to the conception and design of the research; John R. Wingard, Zeina A. Al-Mansour, Nosha Farhadfar, Jenna N. Schulz, K.H. McGee, Precious D. Williams, and Christina L. Cline contributed to the acquisition of the data; Michael T. Weaver, John R. Wingard, Wendy J. Dahl, and Jenna N. Schulz contributed to the analysis and interpretation of the data; Wendy J. Dahl, Jenna N. Schulz, and Michael T. Weaver drafted the manuscript; John R. Wingard, Debra Lynch Kelly, and Nosha Farhadfar critically revised the manuscript; and all authors agreed to be fully accountable for ensuring the integrity and accuracy of the work and read and gave final approval for the manuscript.

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CONFLICT OF INTEREST STATEMENT

John R. Wingard has received consultant fees from Cidara, Celgene, Orca, F2G, Takeda; Nosha Farhadfar declares an advisory role for Incyte and Sanofi and is a Chronic GVHD Consortium DSMB member and BMT CTN medical monitor. All other authors declare no conflict of interest.

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