Biol Blood Marrow Transplant 25 (2019) 1382–1386

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Comparing a Neutropenic Diet to a Food Safety-Based Diet in Pediatric Patients Undergoing Hematopoietic Stem Cell Transplantation

Cynthia Taggart[1,2,*], Nicole Neumann[1,2], Priscila Badia Alonso[1], Adam Lane[1], Abigail Pate[1], Audrey Stegman[1], Ava Stendahl[1], Stella M. Davies[1,3], Christopher E. Dandoy[1,3], Michael Grimley[1,3]

[1] *Division of Bone Marrow Transplant and Immune Deficiency, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio*
[2] *Division of Nutrition Therapy, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio*
[3] *Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio*

Article history:
Received 3 January 2019
Accepted 14 March 2019

Key Words:
Neutropenic diet
Low bacterial diet
Hematopoietic stem cell transplant
Bloodstream infections
Nutrition
Supportive care

A B S T R A C T

Neutropenic diets were adopted as a way to decrease the infection risks in immunocompromised individuals, but these diets result in significant restrictions in the variety and types of foods an individual may consume. We used a controlled before-and-after study design in consecutive pediatric and young adult patients who underwent hematopoietic stem cell transplant at our center between January 1, 2014, and December 31, 2014. From January through June, all patients were placed on a traditional neutropenic diet; on July 1, we liberalized the bone marrow transplant (BMT) diet to a modified BMT diet. We compared the incidence of bloodstream infections in the first 100 days post-transplant, incidence of norovirus in the first 100 days, total parenteral nutrition days through day 100, incidence of grade 3 to 4 graft-versus-host disease at day 100, gastrointestinal graft-versus-host disease (any stage), and 100-day overall survival. In addition, we administered an investigator-created survey to evaluate food cravings, nausea, diet limitations, and subjective quality of life. In total, 102 patients underwent hematopoietic stem cell transplant during the study period. Forty-nine (48%) received the neutropenic diet and 53 (52%) the BMT diet. Other than more males receiving the neutropenic diet (67% versus 47%, $P = 0.05$), there were no statistical demographic and outcome differences between the 2 groups. Additionally, 46 subjects (45%) completed the investigator-created questionnaire. There was no difference in the perceived food cravings, nausea, diet limitations, and subjective quality of life between the 2 cohorts. These data demonstrate noninferiority of the modified BMT diet over the traditional neutropenic diet. We believe the food safety-based diet offers a greater variety of food, which may assist in the transition to a normal diet.

BACKGROUND

Nutrition during hematopoietic stem cell transplant (HSCT) has evolved over the past 50 years. In the 1960s, HSCT recipients were placed in a total protective environment, and all items, including clothes and linens, were sterilized prior to being taken into the bone marrow transplant unit. All food was sterilized, and HSCT recipient gastrointestinal tracts were "cleansed" with castor oil and antibiotics [1-3]. The diet order for a patient receiving HSCT was known as the neutropenic diet (also known as the immune-compromised diet, low-bacteria diet, low microbial diet, or sterile diet) [1,4-6].

The neutropenic diet was born out of the theory that if the bacteria in the gastrointestinal tract were reduced, then the risk of bacterial translocation would also be reduced. The thought was that if foods were most likely to contain bacteria on them (ie, fresh fruits and vegetables), they should be eliminated from the diet, therefore decreasing the patient's risk of developing a food-borne illness. If these foods were no longer a component of a patient's diet, then the bacterial content of the gastrointestinal tract would be reduced, leading to a decreased rate of bacterial translocation and fewer bloodstream infections (BSIs) [1,7,8]. However, recent evidence suggests that maintenance and homeostasis of a diverse gut microbiome are associated with decreased rates of graft-versus-host disease (GVHD), BSIs, and overall survival [4,9].

There are few studies, especially in the pediatric HSCT population, comparing the neutropenic diet to a standard hospital diet. We performed a controlled before-and-after evaluation comparing a standard neutropenic diet and a food safety-based diet. The aims of the study were to determine noninferiority of the food safety-based diet to the neutropenic diet; evaluate outcomes, including BSIs, GVHD, and days of total parenteral

Financial disclosure: See Acknowledgments on page 1386.
* Correspondence and reprint requests: Cynthia Taggart, Division of Nutrition Therapy, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, MLC 11027, Cincinnati, OH 45229 USA.
E-mail address: cynthia.taggart@cchmc.org (C. Taggart).

https://doi.org/10.1016/j.bbmt.2019.03.017
1083-8791/

nutrition (TPN) utilization; and compare subjective tolerance of the 2 diets.

METHODS

Institutional review board approval was obtained in the proposed study, which was completed in consecutive pediatric and young adult patients undergoing HSCT at Cincinnati Children's Hospital Medical Center from January 1, 2014, through December 31, 2014. We performed a before-and-after analysis of patients who received the neutropenic diet (January 1, 2014, to June 30, 2014) compared to those receiving a food safety-based diet that we termed the modified bone marrow transplant (BMT) diet (July 1, 2014, to December 31, 2014) (Table 1). Prior to implementation of the modified BMT diet, patients remained on the neutropenic diet throughout their initial hospital stay, but there was some variation between providers, especially in patients with gastrointestinal GVHD. After implementation, all patients >1 year of age received the modified BMT diet, and there were no additional restrictions in patients with gastrointestinal GVHD.

We compared patient demographics, including gender, age at time of HSCT, diagnosis, preparatory regimen, graft, donor and match, and HSCT outcome measures, including 1-year overall survival in the 2 cohorts. To evaluate noninferiority, we compared the incidence of BSIs in the first 100 days, stage 3 to 4 GVHD at day 100, gastrointestinal GVHD (any grade), incidence of norovirus in the first 100 days, and number of days of TPN utilization in the first 100 days post-transplant. Norovirus PCRs are obtained as standard of care in our infectious workup for all patients with diarrhea undergoing HSCT.

To compare tolerance of the 2 diets, we gave patients and parents of children over the age of 1 year at the time of HSCT an investigator-created survey in their primary language (English, Spanish, and Arabic). Survey questions included questions on food cravings, broken down by food groups and taste buds (eg, sweet, salty). Patients were asked to rank food cravings after HSCT as never having cravings through always having cravings (every day). To evaluate the impact of the diets on quality of life, the survey questioned worry/stress related to eating, tolerability of the diet, and adherence to the diet. Subjects could select never, almost never, sometimes, often, and almost always in response. Surveys were not requested from patients due to death (20), less than 1 year of age at time of transplant (8), and TPN dependence (1).

Statistical Analysis

Patient demographics, transplant-related factors, and outcomes were compared between groups using the Fisher exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables.

RESULTS

Of the 102 patients who underwent HSCT during the study period, 49 (48%) received the neutropenic diet and 53 (52%) the modified BMT diet. Thirty-three (67%) males received the neutropenic diet versus 25 (47%) receiving the modified BMT diet ($P = 0.05$). There were no other demographic differences between the 2 groups. Nine patients were under the age of 1 year at the time of transplant (4 prior to intervention, 5 after the intervention) and were likely not affected by the change in diet restrictions (Table 2).

Five patients developed norovirus infection in the first 100 days, 2 (4%) in the neutropenic diet population and 3 (6%) in those receiving the modified BMT diet ($P = 1.00$). BSIs in the first 100 days (35% versus 21%, $P = .13$), death within the first 100 days (4% versus 6%, $P = 1.00$), and average days of TPN in the first 100 days (16.3 versus 19.2, $P = .47$) were similar between those receiving the neutropenic diet and those receiving the modified BMT diet. In the 71 patients who underwent allogeneic HSCT, the incidence of grade 3 to 4 GVHD (25% versus 17%, $P = .56$) and gastrointestinal GVHD (28% versus 17%, $P = .39$) was also similar between the 2 groups (Table 3).

Forty-six patients and caregivers (20 neutropenic patients, 26 modified BMT diet) completed the post-transplant investigator-created survey at an average of 6 months post-transplant (Table 4). We did not see statistically significant differences in patients' and caregivers' recall of foods not tasting the way they remembered and not being allowed to eat the foods they wanted to eat. Food cravings were similar, with the exception of meat, between the 2 groups. Finally, there were no differences in patients' and caregivers' recall in eating more during transplant.

DISCUSSION

This is the first study to compare outcomes in pediatric HSCT patients between a liberalized food safety-based diet (modified BMT diet) to the neutropenic diet. Our data demonstrate that patients on the modified BMT diet had similar outcomes to those on the neutropenic diet. We believe these data demonstrate noninferiority of the modified BMT diet. Additionally, the food safety-based diet offers a greater variety of food, which may assist in the transition to a normal diet. However, the perceived impact of the modified BMT diet was not noted in the follow-up survey questions.

Table 1
Comparison of the Neutropenic Diet and Modified BMT Diet

Neutropenic Diet	Modified BMT Diet
• No fresh fruits or vegetables; canned and frozen are allowed	• Fresh fruits and vegetables allowed, including raspberries and strawberries
	• Fresh fruit and vegetables must be well washed under cold running water
	• Families are encouraged to select fruit and vegetables without visible damage (eg, cuts and bruises)
• Pasteurized milk products allowed	• Pasteurized milk products allowed
• Well-cooked eggs allowed	• Well-cooked eggs allowed
• No soft serve ice cream/frozen yogurt served from bulk machines	• No soft serve ice cream/frozen yogurt served from bulk machines
• No raw blue cheese	• No raw blue cheese
• Meats/fish must be cooked well done	• Meats/fish cooked to an internal temperature of 165 degrees or higher (meat thermometer given)
• No undercooked or raw meats/seafood	
• No deli counter meats	
• Packaged lunch meats must be cooked in the microwave for 15 seconds	• No undercooked or raw meats/seafood
	• No deli counter meats; packaged lunch meats are okay
• Cooked grains allowed	• Cooked grains allowed
• Do not handle raw yeast	• Do not handle raw yeast
• Well water only if it is boiled	• Well water only if it is boiled
• No buffet line meals	• No buffet line meals
• Fast-food restaurants—food must be prepared fresh	• Fast-food restaurants—food must be prepared fresh
• No raw honey	• No raw honey
• No sharing drinks or food with family/friends	• No sharing drinks or food with family/friends

Table 2
Demographics of Patients Included in the Study (n = 102)

Demographics	Neutropenic Diet (n = 49)	Modified BMT Diet (n = 53)	*P* Value
Age, mean (SD), y	11.7 (9.3)	9.2 (7.5)	.14
Male (n = 58)	33 (67)	25 (47)	**0.05**
Diagnosis			.39
• Malignancy (n = 49)	25 (51)	24 (46)	
• Immunodeficiency (n = 27)	12 (25)	15 (28)	
• Marrow failure (n = 13)	7 (14)	6 (11)	
• Benign hematology (n = 9)	2 (4)	7 (13)	
• Genetic (n = 4)	3 (6)	1 (2)	
Preparative regimen			1.00
• Myeloablative (n = 78)	37 (76)	41 (77)	
• Reduced intensity (n = 24)	12 (24)	12 (23)	
Graft			.67
• Bone marrow (n = 58)	30 (61)	28 (53)	
• PBSC (n = 40)	17 (35)	23 (43)	
• Cord (n = 4)	2 (4)	2 (4)	
Donor			.53
• Autologous (n = 31)	13 (27)	18 (34)	
• Allogeneic (n = 71)	36 (73)	35 (66)	
Match (allogeneic)			.46
• Matched related donor (n = 26)	11 (31)	15 (43)	
• Matched unrelated donor (n = 27)	16 (44)	11 (31)	
• Mismatched unrelated donor (n = 18)	9 (25)	9 (26)	

Values are presented as number (%) unless otherwise indicated.
PBSC indicates peripheral blood stem cell.
Bold represents significant *P* value.

Recently, Moody et al. [10] performed a randomized control trial, which showed no influence of the neutropenic diet on infection rates in pediatric oncology patients (non-HSCT). Further, a recent meta-analysis including randomized control trials revealed no superiority of the neutropenic diet at reducing mortality or BSIs in adult patients with cancer [11]. However, when the authors analyzed fever or infection as a composite outcome, the hazard ratio was significantly higher in the neutropenic diet arm (relative risk, 1.18; 95% confidence interval, 1.05-1.34; $P = .01$).

The neutropenic diet eliminates food groups, putting patients at risk for nutritional deficiencies and decreased quality of life [4,11,12]. Pediatric bone marrow transplant patients are at significant risk for developing food aversions and vitamin deficiencies since fruit and vegetable consumption is significantly reduced with the neutropenic diet. The neutropenic diet is associated with increased gastrointestinal side effects and decreased vitamin C and fiber, both of which are found in fresh fruits and vegetables [13].

The human diet is one of the most fundamental factors in the development of the human gut microbiome from infancy to the through adulthood. Several studies have shown that dietary changes induce transient fluctuations in the adult microbiome sometimes in as little as 24 hours [14]. Changes related to weight loss and diet composition can also alter the relative abundance of gastrointestinal commensal organisms [15]. The gastrointestinal commensal organisms live in a symbiotic relationship with their host and have a critical function in maintaining gastrointestinal epithelial and immune homeostasis; commensal organisms importantly function to prevent overgrowth of pathogens [16] and provide protective responses against pathogenic bacteria from invading the gastrointestinal mucosa [17].

Patients undergoing HSCT are at risk of developing loss of commensal diversity and a concomitant shift and expansion of pathogenic bacteria (*Lactobacillus* and *Enterobacteria*), and the etiology of these shifts may be related to changes in nutritional intake along with antibiotic exposure [18]. The expansion of pathogenic bacteria, in the setting of an injured gastrointestinal

Table 3
Outcomes of Patients Included in the Study (n = 102)

Outcomes	Neutropenic Diet	Modified BMT Diet	*P* Value
All patients	(n = 49)	(n = 53)	
• Norovirus in first 100 days (n = 5)	2 (4)	3 (6)	1.00
• Bloodstream infections in first 100 days (n = 28)	17 (35)	11 (21)	.13
• Death within 100 days (n = 5)	2 (4)	3 (6)	1.00
• Days on TPN in the first 100 days, mean (SD)	16.3 (18.1)	19.2 (22.6)	.47
Allogeneic patients (n = 71)	(n = 36)	(n = 35)	
• Grade 3-4 GVHD (n = 15)	9 (25)	6 (17)	0.56
• GI GVHD (n = 16)	10 (28)	6 (17)	0.39

Values are presented as number (%) unless otherwise indicated.
GI indicates gastrointestinal.

Table 4
Comparison of Food Taste and Cravings (n = 46)

Characteristic	Neutropenic Diet (n = 20), No. (%)	Modified BMT Diet (n = 26), No. (%)	*P* Value
Foods not tasting the way they were remembered			.89
• Never/almost never	3 (15)	3 (12)	
• Sometimes	6 (30)	7 (27)	
• Often/almost always	11 (55)	16 (61)	
Not being allowed to eat the foods you want to eat			.91
• Never/almost never	9 (45)	13 (50)	
• Sometimes	7 (35)	9 (35)	
• Often/almost always	4 (20)	4 (15)	
Food cravings: salty foods			.65
• Never/almost never	4 (20)	8 (31)	
• Sometimes	6 (30)	8 (31)	
• Often/almost always	10 (50)	10 (38)	
Food cravings: sweet foods			.82
• Never/almost never	9 (45)	14 (54)	
• Sometimes	5 (25)	5 (19)	
• Often/almost always	6 (30)	7 (27)	
Food cravings: bread			.42
• Never/almost never	8 (40)	6 (24)	
• Sometimes	7 (35)	10 (38)	
• Often/almost always	5 (25)	10 (38)	
Food cravings: meat			**.02**
• Never/almost never	3 (15)	11 (42)	
• Sometimes	9 (45)	3 (12)	
• Often/almost always	8 (40)	12 (46)	
Food cravings: dairy products			.67
• Never/almost never	7 (35)	6 (23)	
• Sometimes	5 (25)	8 (31)	
• Often/almost always	8 (40)	12 (46)	
Food cravings: fruit			.67
• Never/almost never	6 (30)	5 (19)	
• Sometimes	6 (30)	10 (38)	
• Often/almost always	8 (40)	11 (43)	
Food cravings: vegetables			.47
• Never/almost never	12 (60)	12 (46)	
• Sometimes	6 (30)	8 (31)	
• Often/almost always	2 (10)	6 (23)	
Was the diet during your BMT difficult to follow/enforce?			.26
• Never/almost never	2 (10)	0	
• Sometimes	6 (30)	4 (15)	
• Often/almost always	12 (60)	22 (85)	
Did a less restrictive diet allow you to eat more?			.82
• Never/almost never	6 (30)	6 (23)	
• Sometimes	5 (25)	6 (23)	
• Often/almost always	9 (45)	14 (54)	

Bold represents significant *P* value.

mucosa, as seen in patients after transplant and with GVHD, carries the risk of potential translocation into the bloodstream and development of BSI [19]. The gastrointestinal microbiome is an important modulator of the biology of HSCT [20], preserving the gastrointestinal microbiota during HSCT by minimizing dietary changes, and antibiotic exposure is thought to be valuable in decreasing BSIs secondary to bacterial translocation through an injured gastrointestinal mucosa as well as further development of GVHD.

This study was limited by its small sample size at a single institution, which limits variety in patient and parent opinion. Further, the before-and-after study design is not as effective as a randomized control study, but we feel that these data add to the argument of the abandonment of the neutropenic diet in pediatric HSCT patients.

Currently, no data support the use of the neutropenic diet, but safe food preparation practices should be used for immunocompromised patients. The Food and Drug Administration promotes safe food handling to avoid contamination in hospitalized patients [21,22]. Fresh fruits and vegetables should be adequately washed, raw meats should be separated from other foods, and standardized refrigeration practices should be employed [12]. We believe a modified BMT diet, following Food and Drug Administration guidelines, is safe in pediatric HSCT patients.

ACKNOWLEDGMENTS

Financial disclosure: The authors have nothing to disclose.

Conflict of interest statement: There are no conflicts of interest to report.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.bbmt.2019.03.017.

REFERENCES

1. Fox N, Freifeld AG. The neutropenic diet reviewed: moving toward a safe food handling approach. *Oncology (Williston Park)*. 2012;26(6):572–575.
2. DeMille D, Deming P, Lupinacci P, Jacobs LA. The effect of the neutropenic diet in the outpatient setting: a pilot study. *Oncol Nurs Forum*. 2006;33(2):337–343.
3. Trifilio S, Helenowski I, Giel M, et al. Questioning the role of a neutropenic diet following hematopoetic stem cell transplantation. *Biol Blood Marrow Transplant*. 2012;18(9):1385–1390.
4. Foster M. Reevaluating the neutropenic diet: time to change. *Clin J Oncol Nurs*. 2014;18(2):239–241.
5. Braun LE, Chen H, Frangoul H. Significant inconsistency among pediatric oncologists in the use of the neutropenic diet. *Pediatr Blood Cancer*. 2014;61(10):1806–1810.
6. Jubelirer SJ. The benefit of the neutropenic diet: fact or fiction? *Oncologist*. 2011;16(5):704–707.
7. Wilson BJ. Dietary recommendations for neutropenic patients. *Semin Oncol Nurs*. 2002;18(1):44–49.
8. Moody K, Finlay J, Mancuso C, Charlson M. Feasibility and safety of a pilot randomized trial of infection rate: neutropenic diet versus standard food safety guidelines. *J Pediatr Hematol Oncol*. 2006;28(3):126–133.
9. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;52(4):e56–e93.
10. Moody KM, Baker RA, Santizo RO, et al. A randomized trial of the effectiveness of the neutropenic diet versus food safety guidelines on infection rate in pediatric oncology patients. *Pediatr Blood Cancer*. 2018;65(1).
11. Sonbol MB, Firwana B, Diab M, Zarzour A, Witzig TE. The effect of a neutropenic diet on infection and mortality rates in cancer patients: a meta-analysis. *Nutr Cancer*. 2015;67(8):1230–1238.
12. Wolfe HR, Sadeghi N, Agrawal D, Johnson DH, Gupta A. Things we do for no reason: neutropenic diet. *J Hosp Med*. 2018;13(8):573–576.
13. Maia JE, da Cruz LB, Gregianin LJ. Microbiological profile and nutritional quality of a regular diet compared to a neutropenic diet in a pediatric oncology unit. *Pediatr Blood Cancer*. 2018;65(3).
14. Wu GD, Chen J, Hoffmann C, et al. Linking long-term dietary patterns with gut microbial enterotypes. *Science*. 2011;334(6052):105–108.
15. Voreades N, Kozil A, Weir TL. Diet and the development of the human intestinal microbiome. *Front Microbiol*. 2014;5:494.
16. Taur Y, Pamer EG. The intestinal microbiota and susceptibility to infection in immunocompromised patients. *Curr Opin Infect Dis*. 2013;26(4):332–337.
17. Hill DA, Artis D. Intestinal bacteria and the regulation of immune cell homeostasis. *Annu Rev Immunol*. 2010;28:623–667.
18. David LA, Maurice CF, Carmody RN, et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature*. 2014;505(7484):559–563.
19. Ubeda C, Taur Y, Jenq RR, et al. Vancomycin-resistant Enterococcus domination of intestinal microbiota is enabled by antibiotic treatment in mice and precedes bloodstream invasion in humans. *J Clin Invest*. 2010;120(12):4332–4341.
20. Docampo MD, Auletta JJ, Jenq RR. Emerging influence of the intestinal microbiota during allogeneic hematopoietic cell transplantation: control the gut and the body will follow. *Biol Blood Marrow Transplant*. 2015;21(8):1360–1366.
21. Food Facts for Consumers. Accessed 13 December 2018. https://www.fda.gov/food/buy-store-serve-safe-food/food-facts-consumers.
22. Basics for Handling Food Safely. Accessed 13 December 2018. https://www.fsis.usda.gov/wps/portal/fsis/topics/food-safety-education/get-answers/food-safety-fact-sheets/safe-food-handling/basics-for-handling-food-safely/ct_index.