Effects of individualized nutrition after allogeneic hematopoietic stem cell transplantation following myeloablative conditioning; a randomized controlled trial

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Abbrevations: aGVHD, acute graft-versus host-disease; allo-HSCT, allogeneic hematopoietic stem cell transplantation; EN, enteral nutrition; MAC, myeloablative conditioning; OM, oral mucositis; PN, parenteral nutrition; QoL, quality of life; RCT, radndomized controlled trial; RIC, reduced intensive conditioning; TPN, total parenteral nutrition.

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SUMMARY

Background & aims: Reduced quality of life (QoL) is prevalent after allogeneic hematopoietic stem cell transplantation (allo-HSCT). In this randomized trial we examined the effect of individualized nutritional support during hospitalization for allo-HSCT. Primary outcome was change in global QoL three months post-HSCT with oral mucositis (OM) and acute graft-versus-host disease (aGVHD) as main secondary outcomes.

Methods: Whereas the intervention group received recommended minimum daily intakes of 126 kJ/kg and 0.75 g protein/kg as food, supplements, enteral or parenteral nutrition, the controls received routine feeding. QoL was self-reported using the EORTC QLQ-C30 questionnaire.

Results: Between August, 2010 and February, 2016, we randomized 59 and 60 patients to intervention and control, respectively; 40 and 48 being eligible for analysis of QoL. There was no difference between the two groups in mean global QoL after three months (-3.10, 95% CI -11.90-5.69; *P*=0.49). Nor were there any differences in OM grades 3-4 (RR (vs grades 0-2), 1.11, 95% CI 0.59-2.11 and 0.95, 95% CI 0.72-1.25, respectively; *P*=0.78), or aGVHD grades 3 or 4 (RR (vs grades 0-2) 0.44, 95% CI 0·12-1.60; and 0.65, 95% CI 0.20-2.20, respectively; *P*=0.37).

Conclusion: Individualized nutritional support with recommended energy and protein intakes during hospitalization had no effect on QoL, OM or aGVHD three months after allo-HSCT compared to routine nutrition.

Keywords:

- Allogeneic hematopoietic stem cell transplantation.
- Quality of life.
- Nutritional support.
- Nutritional status.
- Oral mucositis.
- Graft-versus-host disease.

1. Introduction

Weight loss and malnutrition are frequent following allogeneic hematopoietic stem cell transplantation (allo-HSCT) [1]. The patients typically experience nausea, vomiting, sore mouth, taste changes, loss of appetite and fatigue [2]. These symptoms are more intense after myeloablative conditioning (MAC) compared to reduced-intensity conditioning (RIC), and they are associated with impaired QoL [2, 3]. Nutritional support may alleviate these symptoms and thus improve QoL, however, the evidence for such an effect is weak [4]. One randomized controlled trial (RCT) reported improved survival in allo-HSCT recipients receiving total parenteral nutrition (TPN) compared with an electrolyte-enriched solution in allo-HSCT recipients [5]. However, there is no conclusive evidence of the use of TPN versus parenteral nutrition (PN) or enteral nutrition (EN) on other outcomes [6-9]. Furthermore, a significant association between severe acute graft-versus-host disease (aGVHD) and poor oral intake has been reported [10]. As EN is thought to preserve the integrity of the gut mucosa and reducing infections, EN is recommended when the gut resumes normal function [4, 11].

Up to three months after myeloablative conditioning, allo-HSCT patients score high on nutrition-related symptoms known to impair QoL [2, 3]. Importantly, no evidence-based recommendations exist on when and how to best provide nutritional support, and there are no RCTs with a tailored nutritional intervention to allo-HSCT patients with QoL as the main outcome. The primary aim of our study was therefore to examine if individualized nutritional support could change global QoL three months after allo-HSCT compared to routine nutritional support. Main secondary outcomes were occurrence and duration of oral mucositis (OM) grades 3 and 4 and occurrence of aGVHD grades 3 and 4.

2. Methods

Patients ≥18 years admitted for allo-HSCT with MAC at Oslo University Hospital for a hematological malignancy were eligible. Exclusion criteria were previous allo-HSCT and inability to consent and/or to follow the trial protocol. The study was approved by the Regional Committee for Medical and Health Research Ethics South East Norway (#S-09136c 2009/2115) and the Data Protection Supervisor, Oslo University Hospital and registered at ClinicalTrials.gov, ID NCT01181076. All patients provided written, informed consent.

2.1. Procedures

Eligible patients were informed about the study at their last visit before allo-HSCT and recruited upon admission for transplantation. A computer-generated 1:1 block randomization (block size 10; www.randomization.com) was used.

All patients received MAC with either (i) busulphan and cyclophosphamide; or (ii) total body irradiation and cyclophosphamide. GVHD prophylaxis was cyclosporine and methotrexate. From day -7 to day -1 before the transplantation, patients received hydration with 5% glucose.

The study period started when commencing conditioning and continued until hospital discharge. For the intervention group the aim was a minimum daily energy intake of 126 kJ (30 kcal)/kg body weight and protein intake of 1.5-2.0 g protein/kg body weight [12, 13]. The target energy intake was validated by measuring resting energy expenditure using indirect calorimetry [14]. An activity factor of 1.4 was used to calculate total energy expenditure [15]. At inclusion the patients received routine hospital food and were encouraged to eat energy-enriched and lactose-reduced snacks and oral supplements on a daily basis. A nasoenteric tube (Flocare Bengmark Ch 8, Nutricia, Schiphol, The Netherlands

or Freka Endolumina 10 Fr, Fresenius Kabi, Bad Homburg, Germany) was inserted between days +3 and +5 [16, 17]. Nutrison Advanced Peptisorb (Nutricia) was used for enteral feeding [16, 17]. The enteral solution consisted of hydrolyzed medium triglyceride fat without fiber, lactose or gluten, and the feeding started at 15 ml/hour and was increased with 15 ml/24 hours (maximum 100 ml/hour), depending on tolerance. Those unable to meet the energy target by the oral or enteral route received the supplementary PN Olimel (OliCliomel Baxter, Illinois) or SmofKabiven (Fresenius Kabi) added micronutrients (10 ml Tracel), and A, B, C, D, E and K-vitamins (Soluvit mixed in 10 ml of Vitalipid Adult). The nurses provided the nutritional supplements based on a predefined algorithm and monitored daily oral, enteral and parenteral energy intake. During hospitalization and outpatient follow-up, the oral energy and protein contents were calculated using the software package Aivo 2000 (AIVO AB, Stockholm, Sweden). After discharge, nutritional advice and oral supplements were provided at the regular outpatient visits.

The control group received routine practice. Energy and protein requirements were not calculated, dietary intake not recorded and enteral feeding was not used. TPN (Olimel or SmofKabiven 1100, 1600 or 2200 kcal/day) was delivered at the discretion of the treating physician to patients unable to eat due to OM. Oral intake was not monitored to avoid increased attention on nutritional intakes among the controls, since participants from both the intervention and control group stayed in the same ward. To obtain proxy-estimates from the controls we therefore included data from an independent reference group (n=13) consecutively recruited and receiving the same nutrition as the control group (Supplemental Panel 1). The patients in both the intervention and control group registered their oral intake one day before the three-month visit.

131 *2.2. Safety monitoring*

132 An independent data monitoring committee evaluated patient safety after hospital discharge
133 for the first 40 patients (20 in each study group), and again after the next 40 patients. No
134 safety concerns were identified.

135

136 *2.3. Assessments of study outcomes*

137 The primary outcome was change in global QoL from baseline to three months post-
138 transplantation assessed by the EORTC QLQ-C30 [18], a cancer-specific 30-item self-report
139 questionnaire consisting of multi-item scales and single-item measures on symptoms and level
140 of functioning. The global QoL score combines two items; overall health and QoL, rated from
141 1 (*very poor*) to 7 (*excellent*) that are transformed to a 0-100 continuous scale. Global QoL
142 was completed at inclusion, at three- and six weeks, and three months post-transplantation.
143 OM was scored with the 0-4 WHO Toxicity Scale [19, 20] from onset of OM until
144 score zero on three consecutive days. Acute GVHD grades 3 and 4 were diagnosed according
145 to the modified Glucksberg criteria [21].
146 Weight was measured with the Tanita BC-418 MA Body Composition Analyzer
147 (Tanita Corp, Tokyo, Japan) read to the nearest 0.1 kg, with the patient wearing light clothes
148 and no footwear. One kg was subtracted to adjust for the weight of clothing. Weight change
149 from baseline to three months were categorized as <5%, 5-10% and >10%. Nutritional status
150 was categorized as well-nourished, moderately malnourished or suspected malnutrition or
151 severely malnourished with the Patient-Generated Subjective Global Assessment tool (PG-
152 SGA) [22]. Fat-free mass index and fat mass index were calculated as fat-free mass and fat
153 mass (kg)/height $(m)^2$. Weight, fat-free mass index and fat mass index were determined at
154 baseline and then repeated at 3 and 6 weeks and at 3 months.
155 Infectious complications were defined as disease due to virus, invasive fungal disease,

bacteremia, pneumonia or empirical use of IV antimicrobial treatment. Cytomegalovirus infection was defined according to Ljungman et al. [23] and fungal disease was classified according to De Pauw et al. [24]. Bacteremia was defined as the first positive blood culture during a 10-day time period. Repeated positive blood cultures obtained >10 days after the first were considered s new episodes. Diagnosis of pneumonia required detection of new pulmonary infiltrates on X-ray or CT scan and symptoms of respiratory infection. Fever was defined as a rectal temperature $\geq$38 °C. All outcomes were registered from any first event until death or discharge from first hospital stay. Neutrophil engraftment was defined as the first of three consecutive days with neutrophil granulocytes $\geq$ 0.2 x 10^9/l and platelet engraftment as platelets > 20×10^9/l without platelet transfusions. Transplant-related mortality was death of any cause except relapse, before three months.

2.4. Statistical analyses

Sample-size calculation was based on an expected change by 15 points in the global QoL score which was considered clinically relevant [25-30] and consistent with our prior results in Norwegian patients with acute myeloid leukemia where global QoL was 60 (SD) [29, 30]. In total, 88 patients (44 in each group) were required to achieve 80% power with a two-sided significance level of 5%.

Results are presented as means (95% confidence intervals [CIs] or SDs), medians and ranges or frequencies (percentages). We used Mann-Whitney U test to test differences between groups in energy and protein intake and length of hospital stay. Analysis of covariance was used to compare differences between the two study groups in global QoL scores at three months adjusting for baseline score [31, 32]. Additionally, the global QoL and subscales scores at all-time points (day -8, three and six weeks and three months) were analysed with a linear mixed model for repeated measures. Subscale scores were

dichotomized (score 0=0 and scores > 0=1) and analyzed by a logistic regression model with general estimating equations when lack of normality was found. We tested for interaction between group and time. Analyses of OM and aGVHD and other secondary outcomes were performed on an intention-to-treat basis. For secondary outcomes we used chi-squared test and estimated relative risks. Nutritional status, infectious complications and transplant-related mortality were analyzed by chi-squared test or Fishers exact test. Weight, fat-free mass index and fat mass index were analyzed with a linear mixed model for repeated measures. Time to engraftment was analyzed by Mann-Whitney U test. A *P*-value <0.05 was considered statistically significant. Analyses were performed using IBM-SPSS 26 (IBM Corp., Armonk, NY).

3. Results

From 2010-2016 we assessed 173 patients for eligibility. Of these, 119 (69%) consented and were randomly assigned to the intervention (n=59) or the control (n=60) group. The median length of hospital stay was 37 (20-104) days in the intervention group and 39 (22-108) days in the control group. None of the patients withdrew, but two patients in the intervention group were excluded from further analyses (Fig. 1). Eighty-eight patients completed the three months' follow-up of QoL (intervention: n=40; control: n=48) while 117 were included in the intention-to-treat analysis of secondary outcomes. Clinical and demographic characteristics are shown in Table 1 and Supplemental Table 1 and 2.

3.1. Energy and protein intake

Energy and protein intakes are shown in Table 2. In the intervention group a gastrointestinal tube was inserted in 55 patients (two refused) and EN commenced in 49 patients (six wanted to remove the tube before commencing EN). The tubes stayed in position a median of 12 (1-50) days. All patients received PN. The median number of days with oral intake, EN, PN and glucose were 27 (6-98), 13 (1-49), 24 (1-78) and 28 (17-64), respectively.

Fifty-nine of 60 control patients received TPN. One patient lacked data on amount and number of days with TPN whereas two received EN as part of intensive care treatment. The median number of days with EN, TPN and glucose was 30 (8-52), 18 (1-84) and 29 (1-98), respectively. In the reference group, median number of days with oral, TPN and glucose were 24 (10-57), 15 (5-27) and 24 (14-35), respectively. There were no significant differences between the controls and the reference group in energy or protein intakes derived from EN, TPN and glucose (Table 2).

214 At three months, energy and protein intakes were available from 72 patients (36 in each
215 study group). The median daily energy intake was 126.0 (134.8-271.6) kJ/kg in the
216 intervention group and 111.8 (162.8-314.4) kJ/kg in the control group (*P*=0.43). The
217 corresponding daily protein intakes were 1.1 (0.3-2.4) g/kg and 1.0 (0.3-2.4) g/kg (*P*=0.51),
218 respectively.
219
220 *3.2. Quality of life*
221 We found no significant differences between the two study groups in the global QoL scores
222 at three months, nor in the subscale scores, except for constipation (Table 3). In both groups
223 significant changes over time was found in global QoL scores and all subscale scores except
224 for dyspnea, constipation and financial difficulties. The global QoL scores were lowest three
225 weeks after transplantation and then improved, though not back to baseline levels. No
226 significant interaction effects were found between group and time for any of the QoL scores
227 (*P*-values 0.08-0.89), except for fatigue (*P*=0.016) with lower scores for the intervention
228 group three weeks after transplantation (Supplemental Table 3).
229
230 *3.3. Secondary outcomes*
231 There were no significant differences between the two study groups in the number of
232 patients with OM grades 3 or 4 or the median number of days with OM grades 3 or 4. The
233 median duration for OM grade 4 was six days in both groups. No significant differences were
234 found between the two study groups regarding the number of patients with aGVHD grades 3
235 or 4 (Table 4) and infectious complications (*P*=0.23-1.00, Supplemental Table 4). We found
236 no significant differences between the intervention, control and reference groups in body
237 weight. In the three groups significant changes over time was found in body weight. Body
238 weight was decreased six weeks after transplantation and was lowest three months after

transplantation. Moreover, there was no significant difference between the intervention and control group in fat-free mass index and fat mass index. In both groups significant changes over time were found in fat-free mass index and fat mass index. Loss of body weight resulted in loss of fat mass (Table 5). No significant interaction effects were found between groups and time for body weight, fat-free mass index or fat mass index (*P*-values 0.08-0.77). From baseline to three months the number of patients experiencing a weight change <5%, 5-10% or >10%, were 22, 11 and 11 in the intervention group, respectively, and 21, 10 and 21 in the control group, respectively (*P*=0.28). The number of patients categorized as well-nourished, moderately or suspected malnourished or severely malnourished at three months, were 28, 11 and 2, respectively, in the intervention group, and 28, 16 and 4 respectively, in the control group (*P*=0.54). The median (range) number of days to neutrophil engraftment was 15 (11–31) in the intervention group and 16 (10–30) among the controls (*P*=0.63). Fifty (87.7 %) patients in the intervention and fifty-three (88.3 %) in the control group were available for analysis of days to platelet engraftment and the median (range) days were 17 (26) and 14 (53), respectively (*P*=1.0). Seven patients in each group had an increased platelet transfusion need, and were excluded from analysis. Nine patients in the intervention group and five controls died before three months (*P*=0.26).

4. Discussion

In this RCT, an individualized nutritional intervention with recommended daily intakes of energy and protein had no superior effect on global QoL three months post-transplant compared to routine nutritional practice. Furthermore, no effects were found on other QoL-outcomes, OM or aGVHD.

This is the first RCT with an individualized nutritional intervention and QoL as the primary endpoint and direct comparisons with previous studies are thus of limited value. One explanation as to why the intervention had no effect on global QoL in our study could be that three months is too short for potentially significant differences to become apparent. Given the aggressive treatment of allo-HSCT after MAC, our results show that most of the scales and single items reflecting physical impairments may still be compromised at three months. This may be reflected in the patient's overall QoL perceptions. In line with our results, no significant improvement has been reported in global QoL three months after transplantation [2, 3]. However, six months post-HSCT an association between physical well-being and higher BMI, and conversely between poorer physical and social well-being and weight loss, were reported in a prospective, longitudinal study [33].

Another potential explanation could be lack of differences between the two study groups in nutritional status at study-end. Patients may have lost weight after discharge. The similar energy intake in both groups at three months despite nutritional counseling in the intervention group upon discharge supports this notion.

Few studies have examined the effect of nutritional intervention on OM or aGVHD. There were no significant differences between the two study groups in frequency or duration of severe OM or severe aGVHD. One prospective [34] and one retrospective observational study [35] compared the effect of EN versus PN on clinical outcomes 100 days post-HSCT with

either MAC [34] or both MAC and RIC [35]. Although neither study found any effects on OM, fewer patients with aGVHD was found in the EN compared to the PN group in one of these studies [34], in contrast to the other [35]. Notably, the actual energy and protein intakes in these two studies were not reported, and about half of the patients in the EN groups received additional PN. Interestingly, a retrospective study of allo-HSCT patients following MAC reported a correlation between increased number of days with no oral intake (i.e. before the diagnosis of aGVHD) and the incidence of severe aGVHD [10].

We found no significant differences in infectious complications between the two study groups. This is partly in line with a previous report [34]. Whether nutritional support influences time to engraftment is not known. In line with a study comparing EN vs PN [35], we found no significant difference in the time to neutrophil engraftment, while earlier neutrophil engraftment has been reported when comparing EN vs PN [34].

We cannot fully exclude the possibility of an unintentional increased focus on nutrition among control patients and staff leading to increased intakes. However, the total energy intake in the intervention group was significantly higher than in the reference group while the amount of energy derived from medical nutrition did not differ significantly between the control and the reference group. It is therefore reasonable to assume that the oral intake among the controls did not exceed that of the reference group. These intake data therefore argue against a similar total intake of energy in the intervention and control group. Furthermore, a low protein intake in the intervention group may potentially explain lack of differences between the two study groups, even if a median protein intake of 1 g/kg/day was achieved in the intervention group, corresponding to the lowest recommended protein intake when we designed the study in 2009 [13].

We chose to include only allo-HCST patients treated with MAC since their nutritional problems due to drug-induced toxicity are more severe [36] and their QoL outcomes more

impaired than after RIC [2]. The nutritional intervention was individualized based on assessment of resting energy expenditure using indirect calorimetry and day-to-day monitoring of food and nutrient intake to ensure accuracy of energy and protein intake. Moreover, the study outcomes were based on validated scoring methods. Furthermore, the lack of intervention effect is probably not explained by non-adherence to the protocol since the targeted minimum of energy and protein intakes per day was achieved for most patients in the intervention group during the hospital stay. A limitation is that our trial was not designed to analyze sub-groups, e.g. single diagnoses or route of nutritional support.

Our trial showed that individualized nutrition targeting recommended daily intakes of energy and protein during hospitalization had no effect on global QoL or QoL subscales three months after allo-HSCT. Moreover, we found no effect of the intervention on nutritional status, OM, aGVHD, infectious complications, time to engraftment or transplant-related mortality. Whether nutritional support in the post-transplant- and rehabilitation phase could improve outcomes, warrants further testing.

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Statement of authorship

KJS designed the study, implemented the intervention, collected and analyzed the data, and drafted the manuscript. MJH designed the study, contributed to data interpretation and specifically supervised the analysis of the QoL results. AB and KEAL contributed to data interpretation and specifically contributed to the design of the intervention. MBV contributed to the interpretation of the data and the statistical analysis. AMG implemented the intervention and contributed to data interpretation. SD and LB contributed to data analyses and interpretation. GET and POI designed the study and analyzed and interpreted the data. All authors prepared and approved the final manuscript.

Conflict of interest

The authors declare no conflict of interests.

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Figure caption

Fig. 1. Flow diagram showing the inclusion process.

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459 # Tables

Table 1

Baseline characteristics.

Characteristic	Intervention (n=57)	Control (n=60)
Age yr – median (range)	45 (19-65)	41 (18-62)
Female – no. (%)	20 (35)	25 (42)
AML – no. (%)	36 (63)	31 (51)
High risk first remission	23	22
After relapse, beginning of first relapse and in second remission	10	9
First remission standard risk	3	-
ALL – no. (%)	6 (10)	10 (17)
First remission high risk	3	7
Early first relapse, second remission	3	3
CML – no. (%)	2 (4)	7 (12)
Chronic phase	-	1
Accelerated phase	2	6
CMML – no. (%)	3 (5)	3 (5)
MDS – no. (%)	6 (11)	5 (8)
Other – no. (%)[1]	4 (7)	4 (7)
Donor – no. (%)		
HLA-identical sibling	17 (30)	13 (22)
HLA-identical unrelated	40 (70)	47 (78)
Stem-cell source – no. (%)		
Bone marrow	25 (44)	27 (45)
Peripheral-blood hematopoietic cells	32 (56)	33 (55)
Sex mismatch[2] – no. (%)	17 (30)	10 (17)
Positive CMV serology – no. (%)		
Donor	27 (47)	24 (40)
Recipients	45 (79)	43 (72)
Conditioning – no. (%)		
Busulphan + Cyclophosphamide	56 (98)	56 (93)
TBI + Cyclophosphamide	1 (2)	4 (7)
HCTI - CI risk groups – no. (%)[1]		
Low risk	42 (74)	45 (75)
Intermediate risk	8 (14)	10 (17)
High risk	7 (12)	5 (8)

Table 1
Baseline characteristics.

Characteristic	Intervention (n=57)	Control (n=60)
EBMT score – no. (%)[1]		
0-3	33 (58)	36 (60)
4	14 (24)	14 (23)
5-7	10 (18)	10 (17)
Performance status ECOG – no. (%)		
0	55 (96)	54 (90)
1	2 (4)	6 (10)
BMI – no. (%)		
Underweight	2 (4)	4 (7)
Normal weight	31 (54)	27 (45)
Overweight	17 (30)	26 (43)
Moderately obese	4 (7)	3 (5)
Severely obese	3 (5)	0 (0)

Abbreviations: AML=Acute myeloid leukemia; ALL=Acute lymphocytic leukemia; CML=Chronic myeloid leukemia; CMML=Chronic myelomonocytic leukemia; MDS=Myelodysplastic syndrome; CMV= Cytomegalovirus; TBI= Total body irradiation; HCTI-CI = Hematopoietic Cell Transplantation-specific comorbidity index [37]; EBMT score = European Group for Blood and Marrow Transplantation score [38]; ECOG = Eastern Cooperative Oncology Group.
[1]An expanded list of baseline values for other diagnosis, EBMT score and HCTI-CI score is provided in Supplemental Table 1.
[2]Sex mismatch was defined as female donor to male recipients.

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Table 2
Daily intake of energy and protein from the day the patient commenced the conditioning regime until hospital discharge.

			Energy intake (kJ/kg body weight)			Protein intake (g/kg body weight)		
Group	n	Days of hospital stay	Total	Oral	Medical Nutrition[1]	Total	Oral	Medical Nutrition[1]
Intervention	57	37 (20-104)	131.9 (58.2-178.7)[*]	52.7 (12.1-126.0)	101.7 (43.5-167.0)	1.1 (0.5-1.5)[*]	0.39 (0.10-0.91)	1.00 (0.52-1.48)
Control	60	39 (22-108)	-	-	74.9 (5.0-147.8)[**]	-	-	0.98 (0.30-1.64)[**]
Reference group	13	32 (22-64)[2]	99.2 (50.2-139.8)	48.6 (15.5-95.0)	64.5 (23.4-137.3)	0.6 (0.4-1.0)	0.27 (0.08-0.61)	0.98 (0.57-1.35)

Values are medians (range).
[1]Sum of glucose, enteral and parenteral nutrition.
[2]Number of days energy and protein intake were registered.
[*]Intervention group compared to the reference group, P=<0.001
[**]Control group compared to the reference group: energy intake P=0.12, protein intake P=0.89.

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Table 3
Comparison of quality of life scores from baseline to three months.

Outcome	Intervention (n=40)		Control (n=48)		Intervention versus control at 3 months*	
	Baseline	3 months	Baseline	3 months	Difference	*P*-value
	Mean (SD)		Mean (SD)		Mean (95% CI)	
Global quality of life	70.4 (17.6)	58.8 (19.2)	69.6 (22.0)	55.4 (23.3)	-3.10 (-11.90 to 5.69)	0.49
Physical functioning	78.3 (14.8)	63.5 (23.6)	80.3 (20.2)	66.6 (23.6)	-2.20 (-7.23 to 11.57)	0.65
Role functioning	51.3 (27.3)	42.9 (29.2)	57.3 (36.5)	39.9 (32.4)	-4.61 (-17.39 to 8.17)	0.48
Emotional functioning	82.7 (15.8)	79.4 (16.6)	83.3 (19.1)	81.5 (21.4)	-1.84 (-5.81 to 9.50)	0.63
Cognitive functioning	80.8 (21.5)	81.7 (18.8)	82.6 (24.8)	80.9 (23.8)	-2.01 (-10.09 to 6.07)	0.62
Social functioning	51.3 (29.1)	48.8 (25.7)	47.2 (30.2)	47.9 (32.9)	0.31 (-9.52 to 10.15)	0.95
Fatigue	41.4 (21.9)	49.2 (25.8)	35.5 (24.4)	53.0 (29.5)	6.70 (-4.28 to 17.67)	0.23
Nausea/vomiting	7.1 (15.0)	16.3 (21.2)	11.1 (16.6)	20.5 (24.1)	11.50 (-1.67 to 24.68)	0.86
Pain	11.3 (19.8)	22.1 (28.3)	9.4 (20.3)	22.2 (32.5)	0.55 (-12.47 to 13.57)	0.93
Dyspnea	24.2 (27.2)	20.0 (23.6)	21.5 (31.1)	24.1 (27.5)	4.97 (-4.96 to 14.91)	0.32
Insomnia	25.0 (28.0)	32.5 (33.3)	22.0 (28.9)	23.6 (27.5)	-7.89 (-20.80 to 5.03)	0.23
Appetite loss	20.8 (25.8)	35.8 (34.9)	16.3 (23.9)	36.8 (34.5)	0.64 (-14.36 to 15.65)	0.93
Constipation	11.7 (22.1)	6.8 (13.6)	14.6 (25.6)	17.0 (25.9)	9.06 (0.67 to 17.45)	0.04
Diarrhea	15.0 (18.4)	32.5 (35.0)	9.0 (16.5)	33.3 (37.7)	2.48 (-13.23 to 18.19)	0.75
Financial difficulties	16.7 (26.1)	17.5 (29.2)	17.4 (33.0)	18.1 (31.5)	0.17 (-10.74 to 11.07)	0.98

*Difference between the intervention and control group at 3 months adjusted for baseline by analysis of covariance.

Table 4
Severe oral mucositis and acute GVHD.

Outcome	Intervention (n=57)	Control (n=60)	Relative risk (95% CI)	*P*-value
Oral mucositis – no. (%)				0.78
Grades 0-2	15 (26)	15 (25)	Reference	
Grade 3	12 (21)	10 (17)	1.11 (0.59 - 2.11)	
Grade 4	30 (53)	35 (58)	0.95 (0.72 - 1.25)	
Acute GVHD – no. (%)				0.37
Grades 0-2	50 (88)	47 (78)	Reference	
Grade 3	3 (5)	7 (12)	0.44 (0.12 – 1.60)	
Grade 4	4 (7)	6 (10)	0.65 (0.20 – 2.20)	

Table 5
Body weight, fat-free mass index and fat mass index during the study period

Outcome	Intervention group		Control group		Reference group		*P*-value*	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	Group effect	Time effect
Body weight								
Baseline	57	77.7 (16.2)	60	75.9 (15.2)	13	73.8 (15.5)		
3 weeks	52	77.2 (15.3)	59	75.0 (14.4)	12	73.5 (18.0)		
6 weeks	50	73.4 (14.1)	58	71.5 (13.8)	11	70.9 (18.6)		
3 months	44	72.8 (14.6)	52	70.6 (14.1)	7	70.4 (18.2)	0.32	<0.001
Fat-free mass index								
Baseline	56	18.5 (3.1)	59	18.2 (2.5)	-	-		
3 weeks	48	19.2 (3.1)	55	19.1 (3.1)	-	-		
6 weeks	38	18.2 (2.9)	42	18.3 (2.9)	-	-		
3 months	39	18.5 (3.0)	48	18.5 (3.0)	-	-	0.59	<0.001
Fat mass index								
Baseline	56	6.2 (3.0)	59	6.2 (3.0)	-	-		
3 weeks	48	5.6 (3.1)	55	5.0 (3.0)	-	-		
6 weeks	38	5.2 (2.8)	42	4.6 (3.1)	-	-		
3 months	39	4.7 (2.7)	48	4.1 (2.7)	-	-	0.52	<0.001