Comparison of Nutrition-Related Adverse Events and Clinical Outcomes Between ICE (Ifosfamide, Carboplatin, and Etoposide) and MCEC (Ranimustine, Carboplatin, Etoposide, and Cyclophosphamide) Therapies as Pretreatment for Autologous Peripheral Blood Stem Cell Transplantation in Patients with Malignant Lymphoma

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Background:
The aim of this study was to compare nutrition-related adverse events and clinical outcomes of ifosfamide, carboplatin, and etoposide regimen (ICE therapy) and ranimustine, carboplatin, etoposide, and cyclophosphamide regimen (MCEC therapy) instituted as pretreatment for autologous peripheral blood stem cell transplantation.

Material/Methods:
We enrolled patients who underwent autologous peripheral blood stem cell transplantation between 2007 and 2012. Outcomes were compared between ICE therapy (n=14) and MCEC therapy (n=14) in relation to nutrient balance, engraftment day, and length of hospital stay. In both groups, we compared the timing of nutrition-related adverse events with oral caloric intake, analyzed the correlation between length of hospital stay and duration of parenteral nutrition, and investigated the association between oral caloric intake and the proportion of parenteral nutrition energy in total calorie supply. Five-year survival was compared between the groups.

Results:
Compared with the MCEC group, the ICE group showed significant improvement in oral caloric intake, length of hospital stay, and timing of nutrition-related adverse events and oral calorie intake, but a delay in engraftment. Both groups showed a correlation between duration of parenteral nutrition and length of hospital stay (P=0.0001) and between oral caloric intake (P=0.0017) and parenteral nutrition energy sufficiency rate (r=−0.73, P=0.003; r=−0.76, P=0.002). Five-year survival was not significantly different between the groups (P=0.1355).

Conclusions:
Our findings suggest that compared with MCEC therapy, ICE therapy improves nutrition-related adverse events and reduces hospital stay, conserving medical resources, with no significant improvement in long-term survival. The nutritional pathway may serve as a tool for objective evaluation of pretreatment for autologous peripheral blood stem cell transplantation.

MeSH Keywords:
Hematopoietic Stem Cells • Length of Stay • Lymphoma

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Background

Today, cancer therapy requires multimodal approaches that include providing patients with nutrition counseling to reinforce oral nutritional interventions, prevent marked weight loss, and help maintain quality of life [1–3] Among all hematopoietic tumors, malignant lymphoma (ML) currently has the highest incidence rate. The risk of developing ML increases after 40 years of age and the overall incidence of ML has been increasing in recent years [4,5], with the incidence in Europe being about twice that in Japan [4,6]. Autologous peripheral blood stem cell transplantation (auto-PBSCT) is a useful salvage therapy for intractable or recurrent ML responsive to chemotherapy [7–10]. However, because auto-PBSCT is performed concurrently with high-dose chemotherapy, oral food intake is greatly diminished by debilitating nutrition-related adverse events [11]. Fortunately, these adverse events can be easily prevented according to recent studies reporting on the prevention of stomatitis by cryotherapy [12,13], the effective suppression of mucositis by glutamine administration [14], and the utility of palifermin, a keratinocyte growth factor, in hematopoietic stem cell transplantation (HSCT) [15].

Because of difficulty with oral intake following HSCT, nutrition therapy should be started early to adequately manage nutritional complications such as loss of body weight (LBW) [3,16]. Nutrition therapy is widely administered to HSCT patients, and at our cancer center, in order to proactively manage nutrition for these patients, our HSCT team uses a nutritional pathway that systematically integrates multidisciplinary nutritional approaches to ameliorate nutrition-related adverse events and meet patient preferences [17–20]. In a previous study of patients who underwent auto-PBSCT, we evaluated and reported on the impact of drug-related and especially nutrition-related adverse events in the digestive tract [21], but we focused mainly on the evaluation of clinical outcomes because no stratification by treatment was performed in the study. To date, the nutritional status of auto-PBSCT patients on a nutritional pathway has not been comprehensively investigated, and methods of nutrition therapy in terms of nutrition intervention outcomes have not been discussed [22–26].

In this retrospective study, we investigated nutrition-related adverse events and clinical outcomes among patients scheduled to undergo auto-PBSCT who were following a nutritional pathway. We also compared the findings between 2 patient groups according to the preparative regimen for auto-PBSCT: those receiving ifosfamide, carboplatin, and etoposide (ICE) therapy and those receiving ranimustine, carboplatin, etoposide, and cyclophosphamide (MCEC) therapy. ICE therapy was developed in 1992 and MCEC therapy in 2010, with the latter now gradually replacing the former [27,28]. In addition, we explored the utility of the nutritional pathway as a tool for objective evaluation of pretreatment with ICE or MCEC therapy.

Material and Methods

Patients

Between 2007 and 2012, 28 patients with ML underwent ICE therapy (n=14; 9 men, 5 women) or MCEC therapy (n=14; 12 men, 2 women) prior to auto-PBSCT at our cancer center. Parenteral nutrition (PN) was terminated by day 100 after transplantation (day 0) in all patients. Inclusion criteria were first auto-PBSCT and an Eastern Cooperative Oncology Group performance status (PS) of 0-1 before the initiation of pretreatment [29].

Treatment regimens

The preparative ICE regimen for auto-PBSCT was ifosfamide 3 g/m^2 from day −5 to day −2, carboplatine 400 mg/m^2 from day −5 to day −3, and etoposide 200 mg/m^2 from day −5 to day −2. The preparative MCEC regimen for auto-PBSCT was ranimustine 200 mg/m^2 day −8 and day −3, carboplatin 300 mg/m^2 from day −7 to day −4, etoposide 500 mg/m^2 from day −6 to day −4, and cyclophosphamide 50 mg/kg from day −3 to day −2 [27,28]. Granisetron was used for antiemesis in both groups.

Evaluation of nutritional pathway parameters and clinical outcomes

The following nutritional pathway parameters and clinical outcomes were evaluated between the day before initiation of pretreatment while on the nutritional pathway (T1) and the day after termination of PN (T2) (Figure 1). 1) Body mass index (BMI) and percent ideal body weight (%IBW) at T1 were measured, and the association between the percent of loss of body weight (%LBW) and daily/total nutrient intake (total caloric and protein intake) for IBW from T1 to T2 was determined. 2) The number of patients with severe%LBW (≥5% in 1 month), total nutrient intake (total caloric and protein intake), caloric intake from PN, and oral caloric intake was calculated for each group [30]. 3) Basal energy expenditure (BEE), which was estimated using the Harris-Benedict equation, and the efficiency of BEE relative to total caloric intake during the study period (BEE caloric percentage) were calculated by a nutritionist, and the association between BEE caloric percentage and%LBW was analyzed [31,32]. 4) The day oral intake resumed (days elapsed since transplantation: 0) and the day of engraftment (neutrophils >500/cm^3) were evaluated. 5) To examine the severity and timing of often overlapping nutrition-related adverse events, grades were determined based on the Japan Clinical Oncology Group's Japanese version of the Common Terminology Criteria for Adverse Events (CTCAE; 2009 revision) [33] and compared between the treatment groups. In the nutritional pathway, the conditions listed in the CTCAE that we refer to as "nutrition-related adverse events"
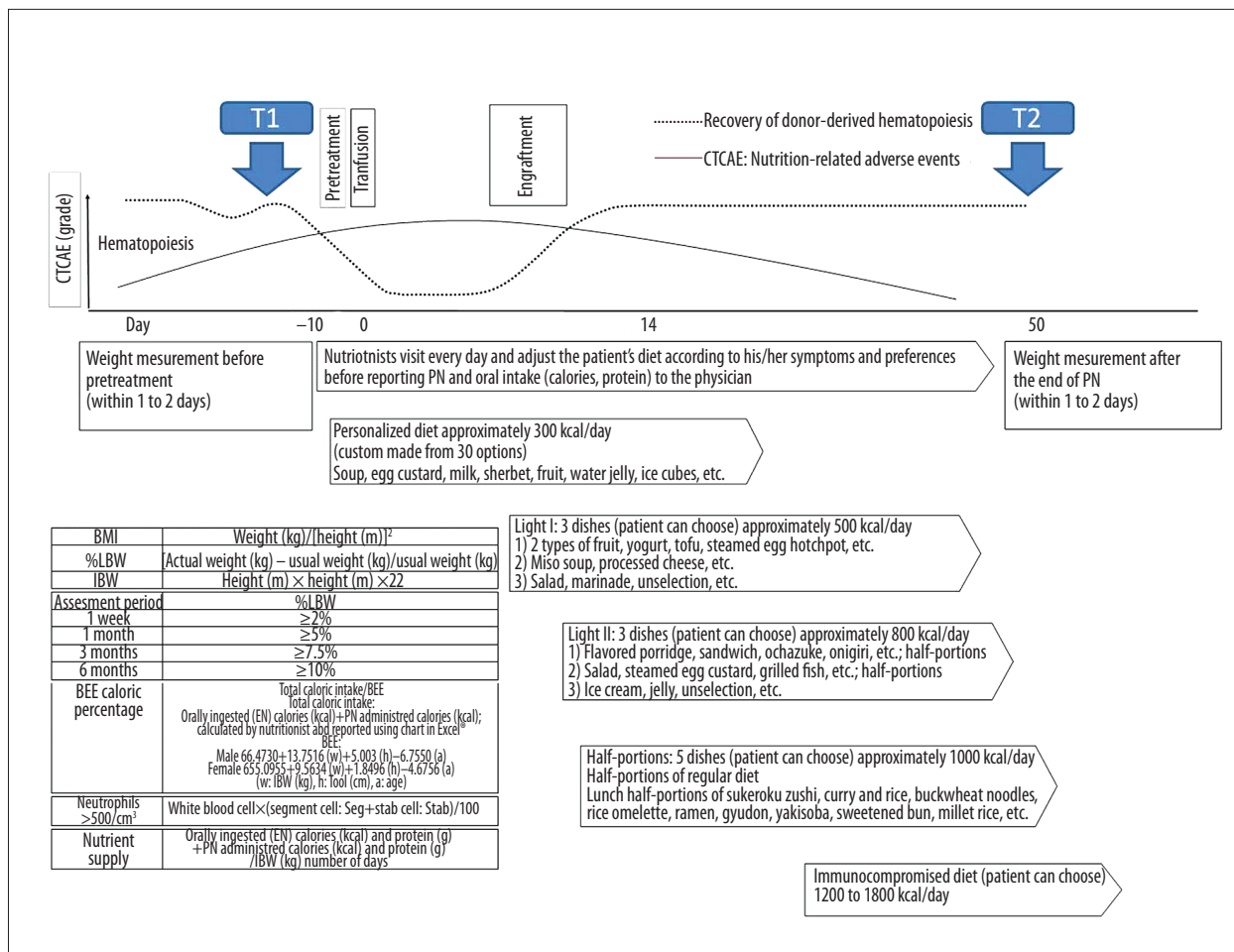
T1 ···· Recovery of donor-derived hematopoiesis
Pretreatment Tranfusion ── CTCAE: Nutrition-related adverse events
Engraftment T2

CTCAE (grade)

Hematopoiesis

Day   −10   0   14   50

BMI	Weight (kg)/[height (m)]²
%LBW	Actual weight (kg) − usual weight (kg)/usual weight (kg)
IBW	Height (m) × height (m) ×22

Assesment period	%LBW
1 week	≥2%
1 month	≥5%
3 months	≥7.5%
6 months	≥10%

BEE caloric percentage
Total caloric intake/BEE
total caloric intake:
Orally ingested (EN) calories (kcal)+PN administred calories (kcal);
calculated by nutritionist and reported using chart in Excel®
BEE:
Male 66.4730+13.7516 (w)+5.003 (h)−6.7550 (a)
Female 655.0955+9.5634 (w)+1.8496 (h)−4.6756 (a)
(w: IBW (kg), h: lool (cm), a: age)

Neutrophils >500/cm³
White blood cell×(segment cell: Seg+stab cell: Stab)/100

Nutrient supply
Orally ingested (EN) calories (kcal) and protein (g)
+PN administred calories (kcal) and protein (g)
/IBW (kg) number of days

Weight mesurement before pretreatment (within 1 to 2 days)

Nutriotnists visit every day and adjust the patient's diet according to his/her symptoms and preferences before reporting PN and oral intake (calories, protein) to the physician

Weight mesurement after the end of PN (within 1 to 2 days)

Personalized diet approximately 300 kcal/day
(custom made from 30 options)
Soup, egg custard, milk, sherbet, fruit, water jelly, ice cubes, etc.

Light I: 3 dishes (patient can choose) approximately 500 kcal/day
1) 2 types of fruit, yogurt, tofu, steamed egg hotchpot, etc.
2) Miso soup, processed cheese, etc.
3) Salad, marinade, unselection, etc.

Light II: 3 dishes (patient can choose) approximately 800 kcal/day
1) Flavored porridge, sandwich, ochazuke, onigiri, etc.; half-portions
2) Salad, steamed egg custard, grilled fish, etc.; half-portions
3) Ice cream, jelly, unselection, etc.

Half-portions: 5 dishes (patient can choose) approximately 1000 kcal/day
Half-portions of regular diet
Lunch half-portions of sukeroku zushi, curry and rice, buckwheat noodles, rice omelette, ramen, gyudon, yakisoba, sweetened bun, millet rice, etc.

Immunocompromised diet (patient can choose)
1200 to 1800 kcal/day

Figure 1. Nutritional pathway in hematopoietic stem cell transplantation (autologous peripheral blood stem cell transplantation). This tool for managing nutrition-related adverse events was used to achieve the treatment outcome of percent of loss of body weight (%LBW) <5% in 1 month. BMI – body mass index; CTCAE – Common Terminology Criteria for Adverse Events; IBW – ideal body weight; BEE – basal energy expenditure; PN – parenteral nutrition; EN – enteral nutrition

(because they hinder oral intake) were vomiting, nausea, anorexia, mucositis/stomatitis, and dysgeusia. Because an actual decrease in food intake is associated with vomiting ≥ grade 1 (G1), nausea ≥G2, anorexia ≥G2, mucositis/stomatitis ≥G2, and dysgeusia ≥G2, these were set as the cutoff values for severity of nutrition-related adverse events (Table 1). To assign a total severity score for each patient, we summed the mean severity score for each nutrition-related adverse event experienced, as noted in the medical records; for example, G3 anorexia (severity score 1) + G1 dysgeusia (severity score 0)=total severity score 1. To examine symptoms that resolved over time, we divided the total daily severity score for each nutrition-related adverse event by the number of participants and presented this as a cumulative graph, then added oral intake percentage to assess as a time-series graph. 6) The associations between length of hospital stay and duration of PN (intervention period) and between oral caloric intake and the PN caloric percentage (energy sufficiency rate of PN relative

to total caloric intake) were analyzed. 7) The 5-year survival rate and number of 5-year survivors were compared between the treatment groups.

Ethical considerations

Written informed consent was obtained from all participants included in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee of Shizuoka Cancer Center (approval no. 27-J99-27-1-3) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Statistical analysis

All assessments used median values (min–max). Weight and nutritional intake were analyzed using Pearson's product-moment correlation coefficient. Severity scores for nutrition-related

adverse events and oral caloric intake were analyzed using Spearman's rank-order correlation. Survival rates were determined from survival curves plotted using the Kaplan-Meier estimator. Significance was set at $P<0.05$. All statistical analyses were performed using JMP version 12.0 (SAS Institute, Cary, NC, USA).

Results

For the 28 patients who underwent auto-PBSCT, the mean BMI was 21.4 kg/m^2 (range, 15.8–30.6 kg/m^2) and the%IBW was 98% (72%–139%). During nutritional pathway intervention,%LBW was −3.3 (−18.0–1.7).

Table 1. Grading of nutrition-related adverse events in CTCAE v3.0 and v4.0.

		Grade 1	Grade 2	Grade 3	Grade4
Vomiting	Version 3.0	1 episode in 24 h	2–5 episodes in 24 h; IV fluids indicated<24 h	≥6 episodes in 24 h; IV fluids, or TPN indicated ≥24 h	Life-threatening consequen
	Version 4.0 Definition: A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth	1–2 episodes (separated by 5 min) in 24 h	3–5 episodes (separated by 5 min) in 24 h	≥6 episodes (separated by 5 min) in 24 h; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated
Nausea	Version 3.0 ALSO CONSIDER: Anorexia; vomiting.	Loss of appetite without alteration in eating habits	**Oral intake decreased without significant weight loss**, dehydration or malnutrition; IV fluids indicated <24 h	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥24 h	Life-threatening consequences
	Version 4.0 Definition: A disorder characterized by a queasy sensation and/or the urge to vomit	Nausea; Loss of appetite without alteration in eating habits	**Oral intake decreased without significant weight loss**, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	–
Anorexia	Version 3.0 ALSO CONSIDER: Weight loss	Loss of appetite without alteration in eating habits	**Oral intake altered without significant weight loss or malnutrition**; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/ or fluid intake); IV fluids, tube feedings or TPN indicated	Life-threatening consequences
	Version 4.0 Definition: A disorder characterized by a loss of appetite	Loss of appetite without alteration in eating habits	**Oral intake altered without significant weight loss or malnutrition;** oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated	Life-threatening consequences; urgent intervention indicated

Table 1 continued. Grading of nutrition-related adverse events in CTCAE v3.0 and v4.0.

		Grade 1	Grade 2	Grade 3	Grade4
Mucositis/ stomatitis (functional/ symptomatic) – Select: Oral cavity	Version 3.0	Upper aerodigestive tract sites: Minimal symptoms, normal diet; minimal respiratory symptoms but not interfering with function	Upper aerodigestive tract sites: **Symptomatic but can eat and swallow modified diet**; respiratory symptoms interfering with function but not interfering with ADL	Upper aerodigestive tractsites: Symptomatic andunable to adequately aliment or hydrate orally; respiratory symptoms interfering with ADL	Symptoms associated with lifethreatening consequences
	Version 4.0 Definition: A disorder characterized by inflammation of the oral mucosal	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; **not interfering with oral intake**; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated
Taste alteration (dysgeusia)	Version 3.0	Altered taste but no change in diet	**Altered taste with change in diet** (e.g., oral supplements); noxious or unpleasant taste; loss of taste	–	–
	Version 4.0 Definition: A disorder characterized by abnormal sensual experience with the taste of foodstuffs; it can be related to a decrease in the sense of smell	Altered taste but no change in diet	**Altered taste with change in diet** (e.g., oral supplements); noxious or unpleasant taste; loss of taste	–	–

Severity score: one count range in CTCAE

Table 2 shows patient background and nutrition assessment findings at T1 and T2 in each group. In the ICE therapy and MCEC therapy groups, the mean age was 44 years (range, 22–59 years) and 53 years (range, 17–63 years), respectively. There was no significant difference in preoperative BMI or%IBW at T1 between the groups. The period of evaluation based on the nutritional pathway (i.e., duration between T1 and T2) was 23 days (range, 20–44 days) in the ICE group and 29 days (range, 24–60 days) in the MCEC group. During this period, severe%LBW (≥5% in 1 month) was observed in 2 patients in the ICE group and 5 patients in the MCEC group. Oral caloric intake was significantly higher in the ICE group than in the MCEC group (18 [range, 5–27] *vs.* 8 [range, 3–13] kcal/IBW/day, respectively; *P*=0.0017), and PN caloric intake showed a tendency to be higher (19 [6–29] and 17 [10–28] kcal/IBW/day). In both groups,%LBW was correlated with total caloric and total protein intake (Figure 2). BEE caloric percentage was 112% (range, 79–145%) in the ICE group and 109% (range, 65–137%) in the MCEC group, and was correlated with%LBW in both groups (r=0.54, *P*=0.05; r=0.66, *P*=0.01, respectively; Figure 3).

The day oral intake resumed was significantly earlier in the ICE group than in the MCEC group (day 0 [range, 0–15] *vs.* day 7 [range, 0–17], respectively; *P*=0.0313), while engraftment day was significantly later (day 12 [range, 9–19] *vs.* day 9 [range, 7–11], respectively; *P*=0.0001). Length of hospital stay was significantly shorter in the ICE group (27 [range, 23–48] *vs.* 36 [range, 26–66] days, respectively; *P*=0.0001).

An association was found between oral caloric intake and timing of severe nutrition-related adverse events. In the ICE group,

Table 2. Comparisons between the MCEC group and the ICE group.

	MCEC group (n=14)		ICE group (n=14)		P value*
Study period	Jan 2006–Dec 2010		Sep 2003–Dec 2005		
Sample size (Male/Female)	14	(12/2)	14	(9/5)	0.19
Age, years (min–max)	53	(17–63)	44	(22–59)	0.11
Preoperative BMI, kg/m^2 (min–max)	22.1	(20.0–25.7)	21.3	(15.8–30.6)	0.99
%IBW (min–max)	101	(91–117)	97	(72–139)	0.93
Assessment period, days (min–max)	29 days	(24–60)	23 days	(20–44)	0.07
%LBW (min–max)	−3.9	(−18.0–1.3)	−2.3	(−6.8–1.7)	0.22
Significant%LBW (≥5) cases, n	5		2		0.19
Total caloric intake, kcal/IBW/day (min–max)	24	(16–32)	26	(18–37)	0.23
Total protein intake, g/IBW/day (min–max)	1.1	(0.7–1.4)	1.1	(0.8–1.5)	0.169
BEE caloric percentage, % (min–max)[1]	109	(65–137)	112	(79–145)	0.31
Day oral intake resumed (min–max)[2]	7	(0–17)	0	(0–15)	0.0313
PN calorie percentage, % (min–max)[3]	73	(54–90)	73	(29–95)	0.30
Engraftment day (min–max)[4]	9	(7–11)	12	(9–19)	0.0005
5-year survival, n	13		14		0.6256

BEE – basal energy expenditure; BMI – body mass index; IBW – ideal body weight; ICE – ifosfamide, carboplatin, and etoposide regimen; LBW – loss of body weight; MCEC – ranimustine, carboplatin, etoposide, and cyclophosphamide regimen; PN – parenteral nutrition. [1] Calculated as [total caloric intake/BEE] ×100; [2] Day oral intake began in patients who continued oral intake until T2; [3] Calculated as [PN caloric intake/total caloric intake] ×100; [4] Defined as neutrophils >500/cm^3. * p value comparing before and after the assessment period (Wilcoxon signed-rank test); ** p value (Chi-square test).
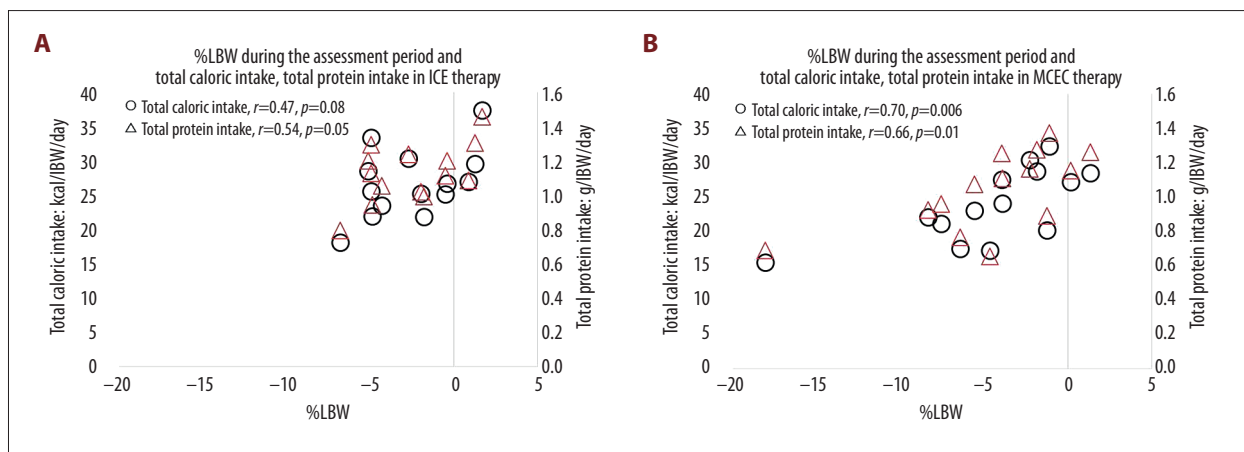

Figure 2. Association of%LBW with total caloric and protein intake in the (**A**) ICE group and (**B**) MCEC group. ○ – total caloric intake; △ – total protein intake. IBW – ideal body weight; %LBW – loss body weight; ICE – ifosfamide, carboplatin, and etoposide regimen; MCEC – ranimustine, carboplatin, etoposide, and cyclophosphamide regimen.

severity score peaked on the day of transplantation (day 0) and decreased thereafter, and thus oral caloric intake was improved (Figure 4, upper panel). In the MCEC group, severity score also peaked at day 0 but, unlike in the ICE group, mucosal disorders persisted, and oral caloric intake did not improve

(Figure 4, lower panel). There was a significant negative correlation between severity score and oral caloric intake in both groups. PN caloric percentage was 73% (29–95%) in the ICE group and 73% (54–90%) in the MCEC group, showing a significant negative correlation with oral caloric intake (r=−0.73,
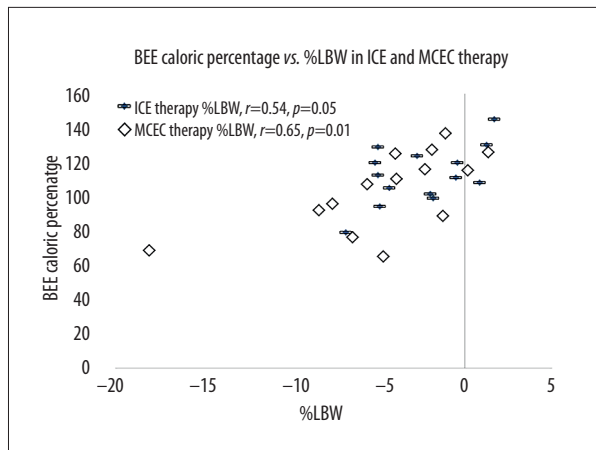
Figure 3. Association between BEE caloric percentage and %LBW in the ICE and MCEC groups. BEE – basal energy expenditure; %LBW – percent of loss of body weight; ICE – ifosfamide, carboplatin, and etoposide regimen; MCEC – ranimustine, carboplatin, etoposide, and cyclophosphamide regimen
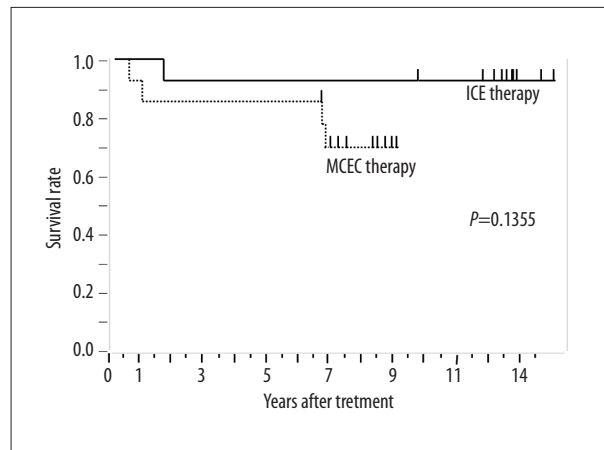

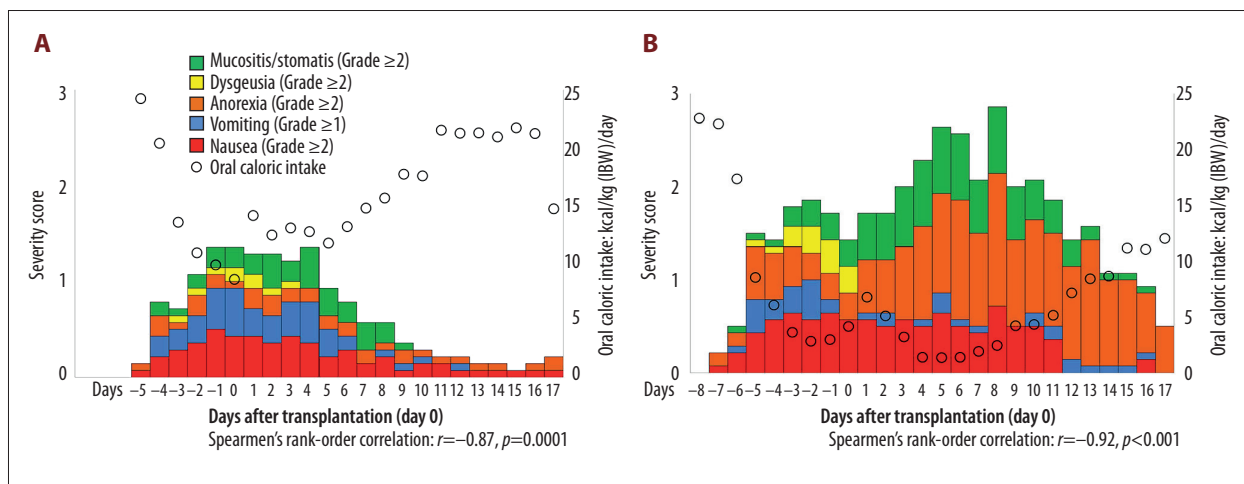**Figure 5.** Survival curves for the ICE and MCEC groups. Solid line: ICE therapy; dotted line: MCEC therapy. ICE – ifosfamide, carboplatin, and etoposide regimen; MCEC – ranimustine, carboplatin, etoposide, and cyclophosphamide regimen.

Figure 4. Association of nutrition-related adverse events with severity score and oral caloric intake in the (**A**) ICE and (**B**) MCEC groups. IBW – ideal body weight; ICE – ifosfamide, carboplatin, and etoposide regimen; MCEC – ranimustine, carboplatin, etoposide, and cyclophosphamide regimen.

P=0.003 and r=−0.76, P=0.002, respectively). There was also a significant correlation between length of hospital stay and intervention period with PN in both groups (ICE: r=0.93, P<0.0001; MCEC: r=0.95, P<0.0001). The number of 5-year survivors was significantly higher in the ICE group (13 *vs.* 10; P=0.4486), but no significant intergroup difference was observed in overall survival (Kaplan-Meier survival curve, P=0.1355; Figure 5).

Discussion

Auto-PBSCT has minimal post-transplant complications associated with various immunological mechanisms, and therefore nutrition-related adverse events occurring after auto-PB-SCT are all attributable to pretreatment chemotherapy. In this study, no significant differences in patient background at pretreatment were observed between the ICE and MCEC therapies. There was a significant difference in oral caloric intake, but total nutrient intake and LBW did not differ significantly between the groups. This suggests that our nutritional pathway intervention offered a similar nutrient balance during both therapies. In all patients, a correlation was observed between %LBW and total caloric intake and protein intake (Figure 2), as well as between %LBW and BEE caloric percentage (Figure 3), suggesting the clinical importance of our nutrition intervention.

In this study, nutrient balance was similar between the two groups; thus, suggesting that resting energy expenditure (REE) decreases in the same manner in ICE and MCEC therapies [34]. To elucidate the factors influencing nutrient metabolism, further study is needed involving accurate measurements of REE by indirect calorimetry [35,36].

In this study, with MCEC therapy, oral intake began significantly later, oral caloric intake was significantly less (suggesting severely impaired oral intake), and consequently PN lasted longer, which in turn prolonged hospital stay. In contrast, engraftment day (representing hematological toxicity in patients) was significantly earlier in MCEC therapy than in ICE therapy. These findings imply that there are clear differences in physical, mental, and economic burden between the two therapies. Patient burden may vary greatly depending on sensitivity to acute toxicity with MCEC therapy, more so than with ICE therapy. However, nutrient balance, 5-year survival rate, and number of 5-year survivors were similar between the two groups (Table 2, Figure 5). Thus, the results of toxicity comparisons in a future study designed using the present nutrition assessment data will be a valuable basis for decision-making in pretreatment chemotherapy. Cyclophosphamide in MCEC therapy and ifosfamide in ICE therapy are alkylating agents with strong emetic effects [37]. The combined use of four different anticancer agents, including cyclophosphamide, in MCEC therapy is thought to be more toxic than the use of three agents in ICE therapy. From the perspective of nutrition science, it would be useful to investigate which regimen, ICE therapy or MCEC therapy, poses a higher risk of gastrointestinal toxicity. We hypothesized that the severity score of both therapies, each comprising various agents, reflects overlap in several nutrition-related adverse events, and quantitative toxicity (measured in terms of oral caloric intake) was observed in the timing of nutrition-related adverse events (severity score) in MCEC therapy (Figure 4). Despite early engraftment and contrary to our expectations, oral mucosal disorder, which interferes with oral intake, lasted longer with MCEC therapy than with ICE therapy. This may be attributable to the total dosage of chemotherapy agents in the regimen. Factors associated with oral mucositis include type of chemotherapy and dosage, and duration of administration. Oral mucositis is a potential side effect of cyclophosphamide, ifosfamide, carboplatin, and etoposide; and carboplatin and etoposide are used in both ICE and MCEC therapies. The same dosage of carboplatin was administered in both therapies, whereas the total dosage of etoposide administered was 800 mg/m^2 in ICE therapy and 1500 mg/m^2 in MCEC therapy, increasing the risk of developing oral mucositis in MCEC therapy. This appears to be the reason for the prolonged oral mucosal disorder in MCEC therapy [38–40].

As in the United States and Europe, Japan has incorporated many outpatient anticancer therapies. Despite the established safety of outpatient chemotherapy [41], the potential of outpatient auto-PBSCT has not been fully explored. A recent study reported no significant difference in the rates of fatal infection between patients treated as outpatients and those treated as inpatients after auto-PBSCT [42]. Furthermore, frequency and duration of neutropenic fever was reduced among outpatients. Given that transplantation medicine is expected to advance further, recommendations have been made to consider performing some forms of transplantation therapy on an outpatient basis [43]. In light of this, it is important to note that both the ICE and MCEC therapies in the present study showed a strong positive correlation between length of hospital stay and PN nutritional pathway intervention and a negative correlation between PN caloric percentage and oral caloric intake. Compared with ICE therapy, MCEC therapy required more medical resources for nutrition therapy. Further evaluation of the health economics involved should produce new information about which of the two is the more appropriate pretreatment choice in HSCT. The utility of the present nutritional pathway can probably be improved by incorporating evaluations of clinical relevance from the perspectives of health economics and treatment-related quality of life.

This study had several limitations. This was a retrospective and non-randomized clinical study with a small number of patients. These patients are currently enrolled in a prospective clinical study we are conducting. Also, we did not assess several nutrition-related factors, such as body composition using bioelectrical impedance analysis. In addition, we did not evaluate adverse events unrelated to nutrition or nutrition-related adverse events from supportive therapy, not nutrition therapy. These issues are being addressed in our current prospective study or will be addressed in future studies.

Conclusions

As pretreatment for auto-PBSCT in patients with ML who were following a nutritional pathway, ICE therapy improved nutrition-related adverse events, reduced hospital stay, conserved medical resources, but had delayed engraftment compared with MCEC therapy. There were no significant differences between the groups in long-term survival, and nutrient balance appeared to be achieved in both groups. With ICE and MCEC, duration of PN and length of hospital stay correlated with oral caloric intake and PN caloric percentage. The effectiveness of these preparative treatments can be evaluated objectively by establishing a nutritional pathway with nutritional intervention that continuously achieves the primary endpoint of prevention of loss of body weight.

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