Original Paper

Annals of Nutrition & Metabolism

Ann Nutr Metab 2016;69:89–98
DOI: 10.1159/000449451

Received: July 14, 2016
Accepted after revision: August 28, 2016
Published online: September 17, 2016

Association of Nutritional Parameters with Clinical Outcomes in Patients with Acute Myeloid Leukemia Undergoing Haematopoietic Stem Cell Transplantation

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Key Words
Myeloid leukemia · Nutrition · Malnutrition · Transplantation

Abstract
Introduction: In acute myeloid leukemia (AML) patients undergoing allogeneic haematopoietic stem cell transplantation (HSCT), there is uncertainty about the extent of influence nutritional parameters have on clinical outcomes. In this study, we investigated the association between initial body mass index (BMI) and weight loss during HSCT on clinical outcomes in a well-characterised cohort of AML patients. ***Methods:*** We analysed data of the Basel stem-cell transplantation registry ('KMT Kohorte') including all patients with AML undergoing first allogeneic HSCT from January 2003 to January 2014. We used multivariable regression models adjusted for prognostic indicators (European Group for Blood and Marrow Transplantation risk score and cytogenetics). ***Results:*** Mortality in the 156 AML patients (46% female, mean age 46 years) over the 10 years of follow-up was 57%. Compared to patients with a baseline BMI (kg/m^2) of 20–25, a low BMI <20 was associated with higher long-term mortality (70 vs. 49%, adjusted hazard ratio 1.97, 95% CI 1.04–3.71, p = 0.036). A more pronounced weight loss during HSCT (>7 vs. <2%) was associated with higher risk for bacterial infections (52 vs. 28%, OR 2.8, 95% CI 0.96–8.18, p = 0.059) and fungal infections (48 vs. 23%, OR 3.37, 95% CI 1.11–10.19, p = 0.032), and longer hospital stays (64 vs. 38 days, adjusted mean difference 25.6 days (15.7–35.5), p < 0.001). ***Conclusion:*** In patients with AML, low initial BMI and more pronounced weight loss during HSCT are strong prognostic indicators associated with lower survival and worse disease outcomes. Intervention research is needed to investigate whether nutritional therapy can reverse these associations.

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Introduction

Loss of appetite resulting in involuntary weight loss is a key symptom of severe illnesses, particularly in different types of malignant diseases [1]. Weight loss associated with malignant diseases may result directly from energy deprivation due to poor appetite and gastrointestinal failure but may also be due to dehydration and sarcopenia [2, 3]. Particularly, the inflammatory response observed in patients with malignant diseases has multiple effects on the brain leading to loss of appetite, as well as on the gastrointestinal tract with delays in gastric emptying [4–6]. Also, endocrine imbalances associated with malignant disease with increases in catabolic hormones (such as glucocorticoid hormones) and a decrease in anabolic hormones (such as testosterone and other sexual steroids) further enhance catabolism and aggravate malnutrition [1]. In addition, anti-cancer therapies may negatively affect nutritional intake due to mucositis and nausea [7]. Importantly, the relationship between malignant disease and cachexia may well be bi-directional, with malignancy and its treatment affecting nutritional status; also malnutrition may have a negative influence on recovery from disease and the course of illness [8, 9].

Patients undergoing allogeneic haematopoietic stem cell transplantation (HSCT) for acute myeloid leukemia (AML) are at eminent high risk for nutritional deterioration. Although AML patients frequently present with a normal nutritional status upon initial diagnosis of disease, they are at risk to experience significant weight loss during HSCT [7]. For this reason, the guidelines of the American and European Societies for Parenteral and Enteral Nutrition (APSEN, ESPEN) stress the importance of using nutrition-screening tools to identify those patients who require formal nutrition assessment with development of a detailed nutrition care plan [2, 3, 10–12]. They also state that nutritional treatment is appropriate in patients undergoing HSCT if they are malnourished at baseline or if it can be anticipated that patients are unable to ingest and/or absorb adequate nutrients for a prolonged period of time. There is, however, uncertainty about the influence of nutritional parameters at baseline and during HSCT on clinical outcomes in specific cancer populations, such as AML patients. Also, it remains unclear who among the patients undergoing HSCT do or do not ultimately benefit from nutritional treatment [13]. Identification of subgroups of patients at highest risk may help to close this gap.

Our aim was therefore to investigate associations of initial body mass index (BMI) and maximal weight loss during HSCT on mortality, and infectious complications in a well-characterised cohort of AML patients included in our patient registry over a 10-year time period. In an exploratory analysis, we also investigated differences in patients with or without nutritional therapy adjusting the analysis for important prognostic indicators.

Methods

Study Design and Setting

This is an observational cohort study including consecutive AML patients enrolled in the Basel stem-cell transplantation registry (KMT Kohorte) for undergoing first allogeneic HSCT from January 2003 to January 2014. Due to the observational character of this study, the Institutional Review Board of the University Hospital Basel (EKNZ) approved the study and waived the need for informed consent.

Study Aims and Hypothesis

The overall study aim was to investigate the interrelatedness of (a) BMI (kg/m^2) before HSCT, (b) weight loss (%) during HSCT, and (c) use of nutritional treatment on different patient-relevant outcomes. We hypothesised that low pre-transplantation BMI and a more pronounced weight loss during HSCT would be strong predictors for adverse outcomes, and that these associations may be reversed by use of nutritional therapy.

Patient Population

We included consecutive patients with a confirmed diagnosis of AML receiving HSCT at the University hospital Basel, Switzerland. This institution has been performing transplantations on patients right from 1973 [14] with a total of more than 2,000 transplantations being performed until now. Clinical practice concerning conditioning regime and supportive therapy has been successively implemented based on results of current research. Patients younger than 16 years were treated at the Universitäts-Kinderspital Beider Basel and were thus not considered for this analysis. Also, patients undergoing reduced-intensity conditioning, patients with other final diagnoses than AML and patients with autologous transplantation were excluded. In addition, we excluded all patients who underwent HSCT before 2003. If patients underwent more than one transplantation process during 2003–2014, only the first transplantation episode was recorded and used for the analysis. From a total of 709 transplantations, 156 were patients with AML fulfilling the study criteria and were thus included in the final analysis.

Definitions and Clinical Variables

All clinical data were used from the KMT cohort file with completion by abstraction from the medical charts. To investigate initial BMI and outcomes, patients were classified as low BMI (<20 kg/m^2), normal BMI (20–25 kg/m^2) and high BMI (>25 kg/m^2). Weight loss during HSCT was defined as the relative difference (%) between initial weight and minimal weight during the hospital stay. Patients were grouped according to their weight loss into little weight loss (<2%), moderate weight loss (2–7%) and high

weight loss (>7%). Patients were also classified as receiving nutritional therapy or not with any route of support counting as having received nutritional therapy. Yet, based on the routine nutritional protocol used in the institution, all patients with nutritional therapy received parenteral nutrition (PE), except for one patient who received complementary enteral nutrition.

For all patients, we calculated the European Group for Blood and Marrow Transplantation (EBMT) risk score as recommended. Genetic risk was also assessed based on the recommendations by the Schweizerische Arbeitsgemeinschaft für klinische Krebsforschung obtained as a result of cytogenetic analyses and grouped into low, moderate or high risk.

Endpoints

The primary endpoint of the study was overall survival until follow-up. Patients were censored at the last time of follow-up if they did not die. Secondary endpoints included in-hospital mortality, mortality within the first 100 days after transplantation, time to engraftment, time to mucositis, time to development of fever (first episode), cumulative number of days with fever, recurrent episodes of fever, infections during hospital stay (including bacterial, viral and fungal infections), recurrence of disease, graft versus host disease (GvHD) of the intestinal tract and the skin, new diagnoses of infections 1 and 2 years after transplantation and secondary cancers within the follow-up period. Aplasia versus engraftment was defined as neutrophil granulocytes $<0.5 \times 10^9$ per litre or $>0.5 \times 10^9$ neutrophil granulocytes per litre, respectively.

Statistical Analysis

This report adheres to the STROBE guidelines for reporting observational studies [15]. Discrete variables are expressed as counts (percentage) and continuous variables as medians and interquartile ranges or means and SD as appropriate. Frequency comparison was done using the chi-square test. To assess the association of our main predictors and outcomes, we used regression models adjusted for main prognostic parameters including the EBMT risk score as well as cytogenetics. Other covariates included age, gender and comorbidities (coronary heart disease, valvular heart disease, congestive heart disease, diabetes, COPD, chronic kidney disease, chronic liver disease). We also adjusted the analysis regarding nutritional therapy with initial BMI and weight loss.

We used cox models for time-to-event data with reporting of hazard ratios (HRs), logistic regression for binary outcomes with reporting of ORs and linear regression for continuous outcomes with reporting of coefficients corresponding to mean differences.

We used STATA 12.1 (Stata Corp 2012, College Station, Tex., USA). All testing was 2-tailed, with $p \leq 0.05$ considered to indicate statistical significance.

Results

Baseline Characteristics

A total of 156 patients (46% women, mean age 46 years) with a confirmed diagnosis of AML were included. The main source of stem cells was peripheral blood (n = 147), but 8 patients received stem cells from bone marrow and one patient received cord blood. The overall mortality rate was 57.1% (n = 89) with a mean time to death of 12 months (95% CI 9–16) and a mean observation time in survivors of 72 months (95% CI 62–82). Table 1 shows patient characteristics of the overall cohort, stratified by overall survival status.

Association of Initial BMI and Outcomes

According to the BMI before HSCT, 71 patients had normal BMI (20–25 kg/m^2), 20 patients had low BMI (<20 kg/m^2) and 65 patients had high BMI (>25 kg/m^2). Overall mortality was significantly increased in patients with a low BMI before HSCT compared to normal BMI (70 vs. 49%) with a HR of 1.97 (95% CI 1.04–3.71, p = 0.036). There was no significant difference in mortality during the index hospital stay and within 100 days. Also, no increase in recurrence risk was found (table 2). When looking at infectious complications during the initial HSCT, low BMI tended to be associated with an earlier development of mucositis (HR 1.72, 95% CI 1.00–3.00, p = 0.051), while fever, fever days and infections had similar patterns of development. Also, outcomes after 1 and 2 years were similar in all groups.

Association of Weight Loss and Outcomes

There was a mean weight loss of 4% calculated from the initial weight before HSCT to the minimal weight during the index hospital stay. A more pronounced weight loss compared to little weight loss (reference group) during HSCT (>7 vs. <2%) was associated with an earlier development of fever (HR 1.92, 95% CI 1.09–3.38, p = 0.025) and more fever days (adjusted difference 3.45, 95% CI 0.59–6.32, p = 0.018), as well as high risk for infectious complications including bacterial infections (52 vs. 28%, OR 2.8, 95% CI 0.96–8.18, p = 0.059) and fungal infections (48 vs. 23%, OR 3.37, 95% CI 1.11–10.19, p = 0.032). Also, the length of stay was significantly increased (64 vs. 38 days, adjusted coefficient 25.6, 95% CI 15.7–35.5, p < 0.001). A more pronounced weight loss was also associated with higher mortality during the index hospital stay (HR 5.59, 95% CI 1.04–29.93, p = 0.044), but results were not significant for mortality within 100 days and overall survival.

Outcomes in Patients Receiving and Not Receiving Nutritional Therapy

In an exploratory analysis, we also investigated outcomes in patients who did receive nutritional treatment with patients who did not receive nutritional therapy. A total of 90 patients (57%) received nutritional treatment

Table 1. Patient characteristics

	All patients	Overall-survivors	Overall-nonsurvivors	p value
Number of patients	156	67	89	
Socio-demographics and nutritional parameters				
Female gender	71 (45.5)	33 (49)	38 (43)	0.42
Age at HSCT, mean (SD)	46.4 (12.0)	45.5 (11.2)	47.1 (12.5)	0.42
Initial BMI, kg/m^2, mean (SD)	24.7 (4.5)	25.0 (4.6)	24.6 (4.4)	0.57
<20	20 (12.8)	6 (9)	14 (16)	0.16
20–25	71 (45.5)	36 (54)	35 (39)	
>25	65 (41.7)	25 (37)	40 (45)	
Lowest BMI, kg/m^2, mean (SD)	23.7 (4.2)	24.1 (4.3)	23.5 (4.1)	0.37
<20	32 (20.5)	11 (16)	21 (24)	0.54
20–25	72 (46.2)	33 (49)	39 (44)	
>25	52 (33.3)	23 (34)	29 (33)	
Weight loss during HSCT, %, mean (SD)	–4.0 (3.0)	–3.5 (2.5)	–4.4 (3.3)	0.077
<2	43 (27.6)	19 (28)	24 (27)	0.42
2–7	90 (57.7)	41 (61)	49 (55)	
>7	23 (14.7)	7 (10)	16 (18)	
Treatment variables				
TBI	42 (26.9)	15 (22)	27 (30)	0.27
One HSCTs	135 (86.5)	61 (91)	74 (83)	0.15
More than one HSCTs	21 (13.5)	6 (9)	15 (17)	
Comorbidities				
Coronary heart disease	7 (4.5)	2 (3)	5 (6)	0.43
Congestive heart failure	8 (5.1)	1 (1)	7 (8)	0.074
Valvular heart disease	9 (5.8)	3 (4)	6 (7)	0.55
Diabetes mellitus	6 (3.8)	3 (4)	3 (3)	0.72
COPD	3 (1.9)	2 (3)	1 (1)	0.40
Chronic kidney disease	5 (3.2)	2 (3)	3 (3)	0.89
Chronic liver disease	17 (10.9)	7 (10)	10 (11)	0.88

Values are n (%) unless otherwise indicated.

during HSCT with all of them being treated with parenteral nutrition (including one patient also receiving complementary enteral nutrition) and 54 patients (60%) receiving also glutamine as part of the nutritional intervention. This analysis was again adjusted for prognostic indicators as well as initial weight and weight loss during the index hospital stay. Compared to not receiving nutritional therapy, receiving parenteral nutrition was associated in the fully adjusted analysis with earlier time to engraftment, but also with worse clinical outcomes including higher mortality, higher risk for fever and infectious complications and also higher GvHD risk (Appendix 1). Also, there was a lower risk for infectious complications during the first and second year after HSCT. Glutamine use compared to using parenteral nutrition without glutamine had similar outcomes except for lower mucositis risk but a fourfold increase in clostridium difficile infection in the adjusted analysis (Appendix 2).

Discussion

Within this cohort of consecutive patients receiving HSCT for AML at a University centre in Switzerland, low initial BMI proved to be a strong and independent risk factor for overall mortality and development of mucositis, while a more pronounced weight loss during HSCT was associated with fever and infectious complications as well as mortality. Importantly, patients with a more pronounced weight loss also showed a marked increase in length of hospital stay that ranged from 28 to 64 days. These data are in line with previous studies from other centres and different patient populations and demonstrate the importance of an impaired nutritional status at the start as well as during HSCT as an unfavourable prognostic factor in this patient population.

Deterioration of nutritional status is a well-known and disease-independent risk factor across medical dis-

Table 2a. Association of initial BMI and outcomes

Outcomes	Normal BMI (20–25 kg/m^2)	Low BMI (<20 kg/m^2)	High BMI (>25 kg/m^2)	p value	Low BMI, multivariable OR/HR (95% CI)	High BMI, multivariable OR/HR (95% CI)*
Therapy outcomes, n	71	20	65			
Engraftment	70 (99)	20 (100)	62 (95)	0.37	HR 1.4 (0.83 to 2.35), p = 0.21	HR 1.22 (0.84 to 1.76), p = 0.291
Mortality during index hospital stay	6 (8)	2 (10)	6 (9)	0.97	HR 1.2 (0.23 to 6.19), p = 0.824	HR 1.09 (0.33 to 3.58), p = 0.884
Mortality within 100 days	9 (13)	6 (30)	10 (15)	0.17	HR 2.35 (0.81 to 6.79), p = 0.115	HR 1.34 (0.53 to 3.43), p = 0.538
Overall mortality	35 (49)	14 (70)	40 (62)	0.16	**HR 1.97 (1.04 to 3.71), p = 0.036**	HR 1.27 (0.79 to 2.05), p = 0.329
Recurrence of disease	31 (44)	9 (45)	28 (43)	0.99	HR 1.43 (0.67 to 3.06), p = 0.353	HR 1.01 (0.58 to 1.73), p = 0.985
Complications associated with initial therapy						
Development of fever	54 (76)	16 (80)	54 (83)	0.60	HR 1.08 (0.61 to 1.91), p = 0.782	HR 1.3 (0.87 to 1.95), p = 0.206
Cumulative number of fever-days, mean (SD)	4.7 (5.8)	5.6 (6.3)	5.2 (5.3)	0.82	Difference 0.62 (–2.26 to 3.51), p = 0.669	Difference 0.74 (–1.28 to 2.76), p = 0.47
Number of recurrent fever episodes, mean (SD)	2.2 (2.0)	2.5 (2.3)	2.3 (2.3)	0.85	Difference 0.16 (–0.94 to 1.26), p = 0.774	Difference 0.37 (–0.40 to 1.13), p = 0.348
Mucositis	52 (73)	18 (90)	52 (80)	0.25	**HR 1.72 (1.00 to 3.00), p = 0.051**	**HR 1.43 (0.95 to 2.14), p = 0.084**
Bacterial infection	57 (80)	16 (80)	48 (74)	0.64	OR 0.95 (0.27 to 3.35), p = 0.931	OR 0.76 (0.33 to 1.77), p = 0.528
Blood stream infection	24 (34)	8 (40)	20 (31)	0.74	OR 1.23 (0.43 to 3.48), p = 0.703	OR 1.03 (0.48 to 2.20), p = 0.938
Catheter-related infection	21 (30)	4 (20)	11 (17)	0.20	OR 0.61 (0.18 to 2.09), p = 0.432	OR 0.49 (0.21 to 1.53), p = 0.102
Clostridium difficile infection	6 (8)	3 (15)	9 (14)	0.54	OR 1.56 (0.34 to 7.21), p = 0.566	OR 1.83 (0.58 to 5.76), p = 0.304
Fungal infection	19 (27)	8 (40)	21 (32)	0.49	OR 1.82 (0.63 to 5.28), p = 0.269	OR 1.19 (0.55 to 2.59), p = 0.66
Hospital-outcomes						
Length of stay (index hospitalisation), mean (SD)	41.5 (19.9)	42.8 (26.5)	42.0 (21.1)	0.97	HR 1.21 (–9.68 to 12.10), p = 0.826	HR 1.12 (–6.49 to 8.74), p = 0.771
Use of parenteral nutrition	42 (59)	16 (80)	32 (49)	0.049	HR 1.54 (0.85 to 2.79), p = 0.153	HR 1.02 (0.63 to 1.67), p = 0.93
Longterm complications						
Intestinal GvHD	24 (34)	6 (30)	21 (32)	0.95	HR 0.85 (0.31 to 2.33), p = 0.751	HR 1.19 (0.62 to 2.25), p = 0.602
GvHD of the skin	46 (65)	12 (60)	33 (51)	0.25	HR 1.56 (0.81 to 2.98), p = 0.182	HR 0.88 (0.53 to 1.44), p = 0.607
Secondary cancers	5 (10)	1 (10)	4 (9)	0.98	OR 0.8 (0.08 to 8.08), p = 0.851	OR 1.07 (0.24 to 4.60), p = 0.928
Infections during the first year	32 (48)	6 (35)	27 (45)	0.62	OR 0.54 (0.17 to 1.65), p = 0.278	OR 0.89 (0.42 to 1.87), p = 0.752
Infections during the second year	21 (50)	3 (38)	14 (37)	0.47	OR 0.71 (0.14 to 3.47), p = 0.668	OR 0.47 (0.18 to 1.25), p = 0.131

* Multivariate model adjusted for EBMT score, genetic information from the underlying disease, age, gender, comorbidities (coronary heart disease, valvular heart disease, congestive heart disease, diabetes, COPD, chronic kidney disease, chronic liver disease). Values are n (%) unless otherwise indicated. Bold refers to p values <0.1.

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Table 2b. Association of weight loss and outcomes

Outcomes	Little weight loss <2%	Moderate weight loss 2–7%	High weight loss >7%	p value	Moderate weight loss, multivariable OR/HR (95% CI)	High weight loss, multivariable OR/HR (95% CI)*
Therapy outcomes, n	43	90	23			
Engraftment	41 (95)	88 (98)	23 (100)	0.50	HR 0.93 (0.63 to 1.36), p = 0.708	HR 1.02 (0.61 to 1.73), p = 0.927
Mortality during index hospital stay	2 (5)	7 (8)	5 (22)	0.057	HR 1.9 (0.38 to 9.46), p = 0.433	**HR 5.59 (1.04 to 29.93), p = 0.044**
Mortality within 100 days	7 (16)	14 (16)	4 (17)	0.98	HR 0.99 (0.39 to 2.48), p = 0.979	HR 1.18 (0.34 to 4.11), p = 0.793
Overall mortality	24 (56)	49 (54)	16 (70)	0.42	HR 0.97 (0.59 to 1.58), p = 0.897	HR 1.43 (0.75 to 2.70), p = 0.275
Recurrence of disease	20 (47)	38 (42)	10 (43)	0.90	HR 0.96 (0.55 to 1.66), p = 0.878	HR 1.11 (0.52 to 2.39), p = 0.79
Complications associated with initial therapy						
Development of fever	30 (70)	73 (81)	21 (91)	0.100	**HR 1.49 (0.97 to 2.29), p = 0.071**	**HR 1.92 (1.09 to 3.38), p = 0.025**
Cumulative number of fever-days, mean (SD)	4.0 (4.8)	4.9 (5.6)	7.4 (6.7)	0.058	Difference 0.92 (–1.14 to 2.98), p = 0.378	**Difference 3.45 (0.59 to 6.32), p = 0.018**
Number of recurrent fever episodes, mean (SD)	1.8 (1.9)	2.1 (1.8)	3.7 (3.1)	0.002	Difference 0.24 (–0.53 to 1.00), p = 0.538	**Difference 1.85 (0.79 to 2.92), p = 0.001**
Mucositis	34 (79)	68 (76)	20 (87)	0.49	HR 1.05 (0.69 to 1.59), p = 0.815	HR 1.45 (0.83 to 2.54), p = 0.191
Bacterial infection	33 (77)	69 (77)	19 (83)	0.82	OR 0.95 (0.40 to 2.28), p = 0.915	OR 1.41 (0.38 to 5.17), p = 0.606
Blood stream infection	12 (28)	28 (31)	12 (52)	0.11	OR 1.12 (0.49 to 2.52), p = 0.792	**OR 2.8 (0.96 to 8.18), p = 0.059**
Catheter-related infection	9 (21)	18 (20)	9 (39)	0.14	OR 0.92 (0.37 to 2.27), p = 0.856	OR 2.38 (0.78 to 2.28), p = 0.13
Clostridium difficile infection	5 (12)	10 (11)	3 (13)	0.97	OR 1.08 (0.33 to 3.53), p = 0.895	OR 1.35 (0.28 to 6.45), p = 0.71
Fungal infection	10 (23)	27 (30)	11 (48)	0.12	OR 1.55 (0.66 to 3.67), p = 0.316	**OR 3.37 (1.11 to 10.19), p = 0.032**
Hospital-outcomes						
Length of stay (index hospitalisation), mean (SD)	38.3 (12.8)	37.9 (17.2)	64.1 (32.5)	<0.001	HR –0.68 (–7.78 to 6.42), p = 0.851	**HR 25.62 (15.73 to 35.50), p < 0.001**
Use of parenteral nutrition	26 (60)	48 (53)	16 (70)	0.34	HR 1.41 (0.86 to 2.32), p = 0.169	HR 1.34 (0.70 to 2.56), p = 0.381
Longterm complications						
Intestinal GvHD	14 (33)	26 (29)	11 (48)	0.22	HR 0.74 (0.38 to 1.449), p = 0.375	HR 1.83 (0.81 to 4.12), p = 0.147
GvHD of the skin	25 (58)	53 (59)	13 (57)	0.98	HR 1.02 (0.63 to 1.66), p = 0.931	HR 1.18 (0.60 to 2.32), p = 0.636
Secondary cancer (1 yes, 0 no)	2 (7)	7 (11)	1 (8)	0.81	OR 1.63 (0.31 to 8.44), p = 0.561	OR 1.36 (0.11 to 16.98), p = 0.812
Infections during the first year	21 (51)	36 (43)	8 (42)	0.68	OR 0.75 (0.35 to 1.61), p = 0.463	OR 0.73 (0.24 to 2.22), p = 0.583
Infections during the second year	10 (40)	24 (44)	4 (44)	0.93	OR 1.25 (0.47 to 3.30), p = 0.658	OR 1.16 (0.25 to 5.44), p = 0.852

* Multivariate model adjusted for EBMT score, genetic information from the underlying disease, age, gender, comorbidities (coronary heart disease, valvular heart disease, congestive heart disease, diabetes, COPD, chronic kidney disease, chronic liver disease). Values are n (%) unless otherwise indicated. Bold refers to p values <0.1.

eases [16]. Considerable efforts have been made to standardize nutritional treatment on an inpatient and outpatient basis. National and international consensus committees developed and published guidelines focusing each on distinct medical conditions and different indications [10, 11, 17–26]. Both societies, ASPEN and ESPEN, have published consensus guidelines on screening and nutritional therapy in patients undergoing HSCT [10, 11]. In brief, these guidelines recommend screening for malnutrition and early nutritional interventions if patients are unable to maintain an adequate nutritional intake (energy and proteins) on their own. It is recommended that enteral nutrition should be the first choice feeding route in all patients with inadequate oral food intake and a functioning gastrointestinal tract [2, 3]; supplemental parenteral nutrition is recommended in patients with inadequate food and enteral intake, for example, patients with severe mucositis (grade >3), ileus, or intractable vomiting [2, 3]. Still, there is lack of interventional data demonstrating who among the patient population would benefit most from nutritional interventions as well as regarding the optimal time point to start nutritional therapy, optimal route and optimal products are to be used [13, 27]. Particularly, the AML patient population has not been studied in great detail. In this study, our analysis focused on nutritional status in AML patients before start of therapy and during HSCT and may help to close this gap.

Our data are in line with previous studies looking at associations of nutritional parameters and outcomes in patients with haematological malignancies. One recent retrospective study from Japan including 145 adult patients who received allogeneic HSCT from 2000 to 2009 reported a step-wise increase in the cumulative incidences of 2-year non-relapse mortality from 3.8% in the normal group up to 27.3% in the severe malnutrition group defined based on the post-HSCT weight loss of >10% [28]. The same researchers also found that underweight patients before HSCT was a risk factor for mortality with a roughly 10% increase in risk [29]. Our data validate these findings focusing on a specific patient group, that is, patients with AML and also reporting a variety of different outcomes including mortality, infectious complications and GvHD among others.

In exploratory analyses, we did also investigate associations of nutritional treatment as well glutamine use with outcomes. Importantly, because deterioration of nutritional status is a strong risk predictor for adverse outcome and patients receiving nutrition support in routine medical care in our analysis are per se at higher complication risk, we adjusted our analysis for important prognostic indicators including the EBMT risk score, cytogenetics and comorbidities, as well as body weight before and during HSCT. In the adjusted analysis, we did not find that nutritional therapy would reduce the risks associated with inadequate nutritional status but that in fact outcomes were worse, and additional glutamine treatment did not show any effects on outcomes. Because of the observational design and residual confounding, the interpretation of these results is challenging, maybe even misleading and, thus, must be considered hypothesis-generating only. Nevertheless, this calls for larger randomised trials to investigate the effects of nutritional interventions in this high-risk patient population to establish causal effects.

This report has limitations. First, this was a retrospective analysis of a prospective monocenter cohort study. Follow-up was based on clinical visits during routine medical care and variable in patients. Second, we focus on weight and weight loss only but did not investigate other nutritional parameters including body impedance analysis among others, which may help to better assess detailed body composition [30]. Third, for our exploratory analysis regarding parenteral nutrition and use of glutamine, patients were not randomised and despite adjustment for important prognostic indicators residual confounding is likely. Therefore, this analysis shows associations but does not suggest causality. Prospective interventional trials are needed to better understand the impact of nutritional interventions in this vulnerable patient population.

In conclusion, in patients with AML, low initial BMI and more pronounced weight loss during HSCT are strong prognostic indicators associated with lower survival and worse disease outcomes. Intervention research is needed to investigate whether adequate nutritional therapy can reverse these associations.

Disclosure Statement

P.S. and Z.S. received research grants from Nestle and Abbott. All other authors confirm that they do not have a conflict of interest associated with this manuscript.

Funding

This study was supported in part by the Swiss National Science Foundation (SNSF Professorship, PP00P3_150531/1) and the Research Council of the Kantonsspital Aarau (1410.000.044).

Appendix

Appendix 1. Association of parenteral nutrition and outcomes

Outcomes	No parenteral nutrition	Parenteral nutrition	p value	Use of parenteral nutrition, multivariable OR/HR (95% CI)*
Therapy outcomes, n	66	90		
Engraftment	62 (94)	90 (100)	0.018	**HR 1.35 (0.95–1.93), p = 0.096**
Mortality during index hospital stay	1 (2)	13 (14)	0.005	**HR 9.48 (1.14–79.04), p = 0.038**
Mortality within 100 days	5 (8)	20 (22)	0.014	**HR 3.06 (1.07–8.77), p = 0.038**
Overall mortality	36 (55)	53 (59)	0.59	HR 1.39 (0.88–2.22), p = 0.162
Recurrence of disease	31 (47)	37 (41)	0.47	HR 1.14 (0.68–1.93), p = 0.618
Complications associated with initial therapy				
Development of fever	43 (65)	81 (90)	<0.001	**HR 1.91 (1.27–2.87), p = 0.002**
Cumulative number of fever-days, mean (SD)	2.2 (2.9)	7.1 (6.3)	<0.001	**Difference 4.83 (3.06–6.61), p < 0.001**
Number of recurrent fever episodes, mean (SD)	1.2 (1.3)	3.1 (2.3)	<0.001	**Difference 1.83 (1.16–2.49), p < 0.001**
Mucositis	34 (52)	88 (98)	<0.001	**HR 5.64 (3.55–8.95), p = 0.000**
Bacterial infection	48 (73)	73 (81)	0.21	OR 1.67 (0.71–3.92), p = 0.236
Blood stream infection	18 (27)	34 (38)	0.17	OR 1.66 (0.76–3.65), p = 0.207
Catheter-related infection	13 (20)	23 (26)	0.39	OR 1.46 (0.61–3.51), p = 0.393
Clostridium difficile infection	4 (6)	14 (16)	0.067	**OR 4.06 (1.11–14.86), p = 0.035**
Fungal infection	13 (20)	35 (39)	0.010	**OR 2.95 (1.26–6.88), p = 0.012**
Hospital-outcomes				
Length of stay (index hospitalisation), mean (SD)	32.9 (9.4)	48.4 (24.8)	<0.001	**HR 14.10 (7.67–20.53), p < 0.001**
Longterm complications				
Intestinal GvHD	12 (18)	39 (43)	<0.001	**HR 2.38 (1.19–4.74), p = 0.014**
GvHD of the skin	28 (42)	63 (70)	<0.001	**HR 1.99 (1.21–3.25), p = 0.006**
Secondary cancer	4 (8)	6 (11)	0.55	OR 1.49 (0.25–8.70), p = 0.658
Infections during the first year	35 (56)	30 (38)	0.031	**OR 0.47 (0.23–1.00), p = 0.049**
Infections during the second year	24 (56)	14 (31)	0.019	**OR 0.35 (0.13–0.94), p = 0.037**

* Multivariate model adjusted for for EBMT score, genetic information from the underlying disease, age, gender, comorbidities (coronary heart disease, valvular heart disease, congestive heart disease, diabetes, COPD, chronic kidney disease, chronic liver disease), initial BMI and weight loss.

Values are n (%) unless otherwise indicated. Bold refers to p values <0.1.

Appendix 2. Association of glutamine use and outcomes in patients with parenteral nutrition

Outcomes	No glutamine	Glutamine	p value	Use of glutamin, multivariable OR/HR (95% CI)*
Therapy outcomes, n	36	54		
Engraftment	36 (100)	54 (100)		**HR 0.52 (0.31 to 0.85), p = 0.009**
Mortality during index hospital stay	5 (14)	8 (15)	0.90	HR 0.81 (0.21 to 3.12), p = 0.754
Mortality within 100 days	9 (25)	11 (20)	0.60	HR 0.53 (0.19 to 1.49), p = 0.230
Overall mortality	22 (61)	31 (57)	0.73	HR 0.88 (0.47 to 1.62), p = 0.678
Recurrence of disease	14 (39)	23 (43)	0.73	HR 0.75 (0.35 to 1.59), p = 0.449
Complications associated with initial therapy				
Development of fever	34 (94)	47 (87)	0.25	HR 0.85 (0.52 to 1.39), p = 0.517
Cumulative number of fever-days, mean (SD)	7.0 (6.3)	7.1 (6.3)	0.96	Difference –0.28 (–3.26 to 2.69), p = 0.850
Number of recurrent fever episodes, mean (SD)	3.0 (2.0)	3.1 (2.5)	0.73	Difference –0.09 (–1.18 to 1.01), p = 0.877
Mucositis	36 (100)	52 (96)	0.24	**HR 0.47 (0.28 to 0.78), p = 0.004**
Bacterial infection	28 (78)	45 (83)	0.51	OR 1.81 (0.53 to 6.16), p = 0.345
Blood stream infection	12 (33)	22 (41)	0.48	OR 1.74 (0.63 to 4.82), p = 0.283

Appendix 2. (continued)

Outcomes	No glutamine	Glutamine	p value	Use of glutamin, multivariable OR/HR (95% CI)*
Catheter-related infection	9 (25)	14 (26)	0.92	OR 1.15 (0.37 to 3.59), p = 0.806
Clostridium difficile infection	2 (6)	12 (22)	0.033	OR 4.15 (0.70 to 24.67), p = 0.118
Fungal infection	14 (39)	21 (39)	1.00	OR 0.92 (0.32 to 2.66), p = 0.881
Hospital-outcomes				
Length of stay (index hospitalisation), mean (SD)	50.3 (26.4)	47.1 (23.8)	0.55	HR –3.86 (–14.35 to 6.64), p = 0.466
Longterm complications				
Intestinal GvHD	13 (36)	26 (48)	0.26	HR 1.21 (0.56 to 2.64), p = 0.628
GvHD of the skin	27 (75)	36 (67)	0.40	**HR 0.56 (0.31 to 0.99), p = 0.047**
Secondary cancers	2 (11)	4 (12)	0.89	OR 2.23 (0.23 to 21.40), p = 0.486
Infections during the first year	4 (12)	26 (55)	<0.001	**OR 14.13 (3.02 to 66.06), p = 0.001**
Infections during the second year	3 (17)	11 (41)	0.087	**OR 7.37 (0.78 to 70.08), p = 0.082**

* Multivariate model adjusted for EBMT score, genetic information from the underlying disease, age, gender, comorbidities (coronary heart disease, valvular heart disease, congestive heart disease, diabetes, COPD, chronic kidney disease, chronic liver disease), initial BMI and weight loss.

Values are n (%) unless otherwise indicated. Bold refers to p values <0.1.

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