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ORIGINAL ARTICLE

Nutritional assessment during allogeneic hematopoietic stem cell transplantation: single centre experience

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Summary

Purpose: *The aim of this study was to analyse the changes in several parameters of nutritional status, acute phase proteins' levels and evaluation of the usefulness of the investigated parameters for qualification for total parenteral nutrition (TPN) during allogeneic hematopoietic stem cell transplantations (HSCT).*

Patients and methods: *The nutritional status was assessed in 24 patients. Biochemical and anthropometric indices of nutritional status as well as body fat and resting energy expenditure were assessed. The levels of acute phase proteins were estimated at the same time. All parameters were evaluated during the day before starting a conditioning regimen, after chemotherapy completion and every 7 days until engraftment, at least 3 times after stem cells infusion. Wilcoxon test and canonical analysis were used for statistical analyses.*

Results: *The measurement of body weight and estimation of transferrin levels can be useful for the nutritional assessment during allogeneic HSCT from sibling donors. Prealbumin level, measured 8 days after the conditioning regimen, can be helpful to make a decision for TPN. Statistically significant differences were found in the levels of biochemical indices of nutritional status and in resting energy expenditure (REE) between patients who received stem cells from the bone marrow and from peripheral blood. Values were lower and decreased earlier after transplantation when bone marrow was the source of HSCT.*

Conclusion: *These findings may indicate that the influence of transplantation procedures over patients' nutritional status is bigger when bone marrow is used as a source of hematopoietic stem cells.*

Key words: allogeneic, bone marrow, hematopoietic stem cell transplantation, nutritional assessment, peripheral blood, total parenteral nutrition

Introduction

HSCT is now a widely used treatment for several malignant and non-malignant disorders, attaining cure in a number of diseases of adults and children. Cells with a rapid turnover such as hematopoietic cells, immature enterocytes and epithelial cells of the oral cavity are well recognized as highly susceptible to the effects of chemotherapy or radiotherapy. Early reactions following HSCT such as mucositis, vomiting, diarrhea and anorexia are well known. These symptoms can be exacerbated due to the development of graft versus host disease, liver or renal insufficiency, leading to malnutrition [1].

In comparison with the well nourished patients, the malnourished ones are less likely to tolerate surgery, radiation, and chemotherapy and more often endure serious complications such as infections, delayed wound healing or fistula formation. Malnourished patients are also hospitalized longer, have a diminished quality of life and lower survival rate than well-nourished patients [2-4]. Increased risk of death in the early post-HSCT period as well as greater nonrelapse mortality can be noticed within underweight patient groups [5-14]. Better-nourished patients have a shorter time to engraftment and less probability of

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infectious complications [4, 5, 15].

Serum albumin level is the following prognostic factor which is needed for evaluation before and during transplantation. The value of this parameter is a predictor of in-hospital death, nosocomial infections and length of hospital stay [7, 16-18]. The same indices are used for nutritional assessment and for monitoring of TPN during HSCT as in other clinical situations. Immunological parameters of malnutrition are solely an exception. They can not be used for the evaluation of the nutritional status because of the type of diseases in which bone marrow transplantation is needed and the type of their treatment with using immunosuppressive drugs [19-23].

While TPN is often given to patients in order to maintain their nutritional status during the peritransplantation period, there is conflicting evidence to support its routine use. TPN is a treatment potentially associated with significant limitations including a fluid overload state and hepatic dysfunction. It can increase the number of catheter-site infections and subclavian vein thromboses, and can delay platelet engraftment and suppress normal appetite. The current practice of the timing of TPN is heterogeneous. In many centres TPN starts only when severe mucositis develops [4]. Because nutritional changes after HSCT have not been well studied there is no consensus dictating which nutritional indices can be considered as risk factors for the development of malnutrition and also useful for establishing optimal candidates and for determining the best time to start TPN. The best indices have to be inexpensive, easy to evaluate and they should be independent from parameters of inflammation like acute phase proteins.

The aim of this study was to analyse:

1. The changes in the parameters of the nutritional status in patients treated with allogeneic HSCT.
2. The changes in acute phase proteins in patients treated with allogeneic HSCT.
3. The usefulness of the investigated parameters for qualification for TPN.

Patients and methods

The hospital Ethics Committee approved the study and patients gave informed consent to participate. The nutritional status was assessed in 24 patients (14 males, 10 females) during allogeneic HSCT from sibling donors. The detailed characteristics of patients are summarized in Table 1. The source of hematopoietic stem cells was bone marrow in 7 and peripheral blood

Table 1. Patient characteristics treated with allogeneic hematopoietic stem cell transplantation

No.	*Sex*	*Age (years)*	*Disease*	*Conditioning regimen*	*Parenteral nutrition*	*Hospital stay (days)*
1	F	23	Myelodysplastic syndrome	Fludarabine, melphalan, alemtuzumab	no	28
2	M	32	Myelodysplastic syndrome	Busulfan, cyclophosphamide	no	30
3	F	36	Myelodysplastic syndrome	Busulfan, cyclophosphamide	no	28
4	M	36	Acute myeloid leukaemia	Busulfan, cyclophosphamide	no	31
5	F	40	Acute myeloid leukaemia	Busulfan, cyclophosphamide	yes	58
6	M	31	Acute myeloid leukaemia	Busulfan, cyclophosphamide	no	30
7	F	24	Acute myeloid leukaemia	Busulfan, cyclophosphamide	yes	34
8	M	27	Acute myeloid leukaemia	Busulfan, cyclophosphamide	no	25
9	F	28	Sarcoma granulocyticum	Busulfan, cyclophosphamide	yes	25
10	M	51	Acute myeloid leukaemia	Busulfan, cyclophosphamide	no	25
11	M	34	Hodgkin's disease	Busulfan, cyclophosphamide	no	23
12	M	40	Aplastic anaemia	Cyclophosphamide, ATG	yes	26
13	F	60	Acute myeloid leukaemia	Busulfan, fludarabine	no	20
14	M	20	Acute myeloid leukaemia	TBI, etoposide, ATG	yes	43
15	F	55	Chronic myeloid leukaemia	Busulfan, fludarabine	no	33
16	M	42	Chronic myeloid leukaemia	Busulfan, cyclophosphamide	no	31
17	M	44	Chronic myeloid leukaemia	Busulfan, cyclophosphamide	no	27
18	F	41	Acute lymphoblastic leukemia	TBI, VP-16, cyclophosphamide	no	26
19	F	45	Acute lymphoblastic leukemia	TBI, VP-16, cyclophosphamide	yes	29
20	M	48	Chronic myeloid leukaemia	Busulfan, cyclophosphamide	yes	27
21	M	42	Chronic myeloid leukaemia	Busulfan, cyclophosphamide	yes	31
22	M	44	Myelodysplastic syndrome	Fludarabine, melphalan, alemtuzumab	no	34
23	M	52	Chronic myeloid leukaemia	Busulfan, cyclophosphamide	no	25
24	F	54	Acute myeloid leukaemia	Busulfan, cyclophosphamide	no	34

F: female, M: male, TBI: total body irradiation, VP-16: etoposide, ATG: antithymocyte globulin in 17 patients. After the conditioning regimen 8 patients had to be treated with TPN due to severe mucositis leading to inability for eating and/or drinking. In two of them this complication was associated with necessity for prolonged hospitalization (more than 5 weeks).

The following parameters of nutritional status were assessed:

A. Biochemical indices of nutritional status
   1. prealbumin (PAB)
   2. transferrin (TRF)
   3. retinol binding protein (RBP)
   4. albumin (ALB)
B. Anthropometric indices
   1. body weight
   2. triceps skinfold thickness
   3. midarm circumference
C. Resting energy expenditure (REE)
D. Body fat (%)

The levels of acute phase proteins such as C-reactive protein (CRP), α1-antitrypsin (AAT), α2-macroglobulin (AAG) and serum precursor of amyloid A (SAA) were estimated at the same time. All of the above mentioned nutritional indices and the acute phase protein levels were evaluated during the day before starting the conditioning regimen (day-x), after chemotherapy completion (before graft was given, day-y), and every 7 days until the engraftment, at least 3 times after stem cells infusion (days: y+7, y+14, y+21). The last measurement was always performed after the engraftment. The Gulick's anthropometric tape and anthropometric dividers were used for assessment of midarm circumference and triceps skinfold thickness, respectively. To measure body fat we used the MALTRON BF-906 device (method of measurement of bioelectroimpedance). The MWE-1 device was used for estimation of REE. The levels of biochemical indices of nutritional status and acute phase proteins were determined with an automated immunonephelometer (IMMAGE 800 Immunochemistry System-Beckman Coulter, which takes advantage of an application of nephelometry to the quantification of antigen or antibody).

Because it is known that alterations in body fluids may significantly affect anthropometric measurements, fluid balance was carefully recorded. TPN (if necessary) started between the 2nd and the 3rd measurement after graft transfusion (8-15 days after chemotherapy). The reason for beginning this therapy was severe mucositis with prolonged period (at least 5 days) of minimal oral intake or weight loss of more than 10% during treatment. TPN discontinued when patients were able to consume at least 50% of their daily requirements orally for 3 consecutive days.

Statistical methods

Results were expressed as median level from the particular days of measurements. Wilcoxon test was used for the statistical evaluation of the data obtained (in order to compare results before chemotherapy with those obtained after the end of the conditioning regimen, i.e. the levels of the investigated parameters on day x vs. day y, y+7, y+14, and y+21, respectively). The correlation between parameters of nutritional status and acute phase proteins was checked to assess whether these indices were reliable indicators of the nutritional status in patients treated with HSCT. This correlation was assessed using canonical analysis.

Results

Initially, all patients had normal parameters of nutritional status and acute phase protein levels, except SAA (maybe because of the presence of central venous catheter; Table 2). The starting value of SAA just ex-

Table 2. Indices of nutritional status and levels of acute phase proteins (median) during allogeneic hematopoietic stem cell transplantation

	X	*Y*	*Y+7*	*Y+14*	*Y+21*	*Y+28*
ALB	3.980	3.610	3.610	3.120	3.010	3.720
RBP	4.99	4.33	4.41	2.56	2.77	5.65
PAB	29.6	26.9	20.8	19.1	18.0	31.9
TRF	210	184	157	145	154	212
AAT	149	167	213	256	260.5	234
AAG	87	98.7	121	129	121	120
CRP	0.35	1.18	4.24	3.79	2.83	0.46
SAA	0.7	2.3	8.9	4,3	2.25	3.6
Weight	80	78	77	80	78	81.5
Arm	31.5	31	30.8	30.6	31.4	33.25
Skinfold	23	21	22	22	24.5	30
Fat	19.7	20.4	17.7	20.3	23.35	20.8
KJ/min	4.3	5.4	5.2	4.9	5.55	5.4

Days of measurement:
X- median value of measured parameter before starting conditioning regimen
Y - median value of measured parameter after the end of conditioning regimen before graft transfusion
Y+7,14,21- median value of measured parameter in following mensurations after graft transfusion, every 7 days until engraftment
Biochemical indices of nutritional status:
ALB- albumin, normal range: 3.5-5.0 g/dL
RBP- retinol binding protein, normal range: 3-6 mg/dL
PAB- prealbumin, normal range: 17-42 mg/dL
TRF- transferrin, normal range: 168-308 mg/dL
Anthropometric indices of nutritional status:
Weight- Body weight (kg)
Arm- midarm circumference (cm)
Skinfold- triceps skinfold thickness (mm)
Fat- body fat (%)
KJ/min- resting energy expenditure
Acute phase proteins:
AAT- α1- antitrypsin, normal range: 110-220 mg/dL
AAG- α2- macroglobulin, normal range: 40-100 mg/dL
CRP- C- reactive protein, normal range: up to 0.8 mg/dL
SAA- serum precursor of amyloid A, normal range up to 0.64 mg/dL

ceeded the upper limit of normal. None of the patients had symptoms or signs of infection. There were no life-threatening complications during the transplantation period. Acute graft versus host disease was not observed during the study. No patient was administered albumin supplement or enteral nutrition.

Indices of nutritional status and acute phase proteins for patients treated with allogeneic transplantation from sibling donors started to change within a period of 8 days after finishing the conditioning regimen. A decrease of ALB, RBP, PAB, TRF on days y+14 and y+21 was observed. TRF was also below normal range on day y+7. All parameters became normal one month after graft transfusion. All values of acute phase proteins increased after chemotherapy. CRP levels started to increase from the day after the end of the conditioning regimen, while AAG and AAT levels from day y+7 and y+14, respectively. All values of acute phase proteins returned to normal on the day of the last measurement. Minimum levels of TRF and RBP were observed in the 3rd and albumin and PAB in the 4th measurement. The highest values of CRP and SAA were seen on day y+7, of ATG on day y+14 and of AAT on day y+21. Statistically significant changes in investigated parameters before and after chemotherapy were noticed mainly in the biochemical indices and acute phase proteins (Table 3). Body weight and midarm circumference were also changed but only in some measurements (weight: day y+7; midarm circumference: day y+21). In canonical analysis only changes of TRF levels, body weight and midarm circumference were independent from those of acute phase proteins (lack of high negative correlation, $r > -0.5$, $p < 0.05$).

PAB level, being measured 8 days after the conditioning regimen, showed in the best way the difference between patients who required or not hospitalization beyond 5 weeks. On that day its level was normal in the group with short hospitalization (less than 5 weeks) and decreased below normal in the group with prolonged hospitalization. In this measurement high negative correlation between PAB and acute phase proteins was observed in neither of the patient groups (canonical analysis, $r > -0.5$, $p < 0.05$).

Comparison of the patient group requiring TPN with the ones who did not need it showed statistically significant difference in the TRF value ($p=0.03$). The levels of TRF were lower in the group of TPN patients. PAB value, being measured 8 days after the conditioning regimen, was helpful again to make a decision for TPN. Its level was below the lower limit of normal in patients who required TPN, while it was normal for patients with no need for this kind of nutritional support.

Measurement of body fat (%), triceps skinfold thickness and REE proved insufficient to assess the nutritional status and support during allogeneic transplantation (Tables 2, 3).

Although the number of patients who received bone marrow was small, we tried to investigate the changes of nutritional status during transplantation, depending on the source of hematopoietic stem cells.

Indices of nutritional status for patients who received hematopoietic stem cells derived from peripheral blood started to change 15 days after finishing the conditioning regimen (Table 4). PAB levels remained within normal range during the study. The minimum level of ALB was observed in the 5th measurement, and RBP and TRF in the 4th one. The maximum value of REE was observed in the 5th measurement. Acute phase proteins' levels for these patients started to in-

Table 3. Comparison of indices of nutritional status and levels of acute phase proteins before and after conditioning regimen for allogeneic hematopoietic stem cell transplantation (Wilcoxon test)

	Y	*Y+7*	*Y+14*	*Y+21*
CRP	0.003513	0.002613	0.001208	0.017296
AAT	0.000656	0.000988	0.000656	0.017296
TRF	0.000893	0.000656	0.000656	0.011724
PAB	0.172858	0.003145	0.002164	0.068713
RBP	0.864706	0.046835	0.000806	0.017296
SAA	0.012042	0.001525	0.005389	0.017966
AAG	0.139766	0.007602	0.001787	0.025069
ALB	0.001967	0.000656	0.000656	0.011724
KJ/min	0.168176	0.028424	0.028424	0.144137
Fat	0.721279	0.722110	0.722110	0.144137
Weight	0.236724	0.012520	0.114138	0.715003
Arm	0.161439	0.202630	0.014488	0.715003
Skinfold	0.610302	0.328072	0.721279	0.721279

For abbreviations see footnote of Table 2

Table 4. Indices of nutritional status and levels of acute phase proteins (median) in patients who received hematopoietic stem cells from peripheral blood

	X	*Y*	*Y+7*	*Y+14*	*Y+21*
ALB	3.940	3.760	3.635	3.255	3.060
RBP	4.93	4.9	3.95	2.97	3.47
PAB	28.7	28.9	20.2	19.2	19.4
TRF	210	197	159	148	159
AAT	154	176	210	243	245
AAG	86.4	101	119	160	147
CRP	0.34	0.41	5.17	3.83	4.35
SAA	1	2.3	6,1	2.95	2.7
Weight	78.5	78	76.5	80	82.5
Arm	32.1	32	31	31.3	33.4
Skinfold	23.5	22	21.5	24	30
Fat	15	17.3	17.2	18.3	21.9
KJ/min	3.75	5.2	4.8	4.85	5.6

For abbreviations see footnote of Table 2 crease from the 3rd measurement. The following parameters reached their maximal levels as follows: CRP, SAA on day y+7, AAG on day y+14, and AAT on day y+21.

Indices of nutritional status for patients who received bone marrow-derived hematopoietic stem cells started to change 8 days after finishing the conditioning regimen (Table 5). The minimum level of ALB was observed in the 4th measurement, and of RBP, PAB and TRF in the 3rd measurement. The maximum value of REE was observed before transplantation (day x) and in the 5th measurement. Acute phase proteins' levels for these patients started to increase from the 3rd measurement. The maximal levels of the following parameters were: for CRP, SAA and AAG on day y+7, and for AAT on day y+21.

Statistically significant differences (Wilcoxon test) in the investigated parameters between these two groups were found in the following cases:

1. RBP - day y+7 (p=0.02)
2. PAB- days: x, y, y+7 (p=0.04, 0.01 and 0.02, respectively)
3. AAT - day x (p=0.01)
4. REE - day y+7 (p=0.01)

Values of RBP, PAB, TRF and REE were lower when bone marrow was the source of hematopoietic stem cells for transplantation. RBP and PAB decreased below the lower limit of normal 8 days after chemotherapy in the bone marrow group, while they were still normal in patients who received peripheral blood-derived stem cells.

Discussion

Despite normal nutritional status upon hospital admission, many patients need nutritional support during transplantation. This is caused by the conditioning regimen, which is composed of high doses of chemo- or radiochemotherapy, leading to nausea, vomiting, diarrhea and severe mucositis. These complications bring to patients' inability of eating and drinking and, coupled with systemic inflammatory responses, can lead to anorexia and cachexia. Thus, nutritional assessment in patients undergoing HSCT is very important and can rationalize nutritional support [24, 25]. Indices currently used to evaluate the nutritional status and support can be affected by nonnutritional variables (infections, sepsis, renal and liver insufficiency etc.). These variables may influence parameters of nutriotional status *per se* or per cytokines and acute phase proteins' levels (which constitute the predominant part of an inflammatory response) [19, 24, 26-30].

We investigated and correlated the changes in the indices of nutritional status and acute phase proteins' levels during allogeneic HSCT from sibling donors. This was done to assess whether these indices are reliable indicators of the nutritional status in allogeneic HSCT patients (canonical analysis).

We found that the estimation of TRF levels and measurement of body weight can be useful for nutritional assessment during allogeneic HSCT from sibling donors. In our study changes in the acute phase proteins were not significantly correlated with changes of TRF levels, as well as with changes of body weight (canonical analysis, $r > -0.5$, $p < 0.05$).

PAB levels, being measured 8 days after the conditioning regimen, showed the best difference between patients who required or not hospitalization beyond 5 weeks and also for patients who needed or not TPN. On that day (day y+7) its level was normal in the group with short hospitalization and decreased below normal in those patients requiring prolonged hospitalization. A similar phenomenon was observed when we compared patients who required or not TPN. PAB level was below the lower limit of normal in patients who required TPN, while it was normal in patients with no need of this kind of nutritional support. In this measurement high negative correlation between levels of PAB and CRP was not observed in both patient groups (canonical analysis). TPN started between the 2nd and the 3rd measurement after HSCT (8-15 days after chemotherapy). Therefore, the PAB value that was checked 8 days after the conditioning regimen can function as index for predicting malnutrition development after transplantation.

Thus, our study didn't confirm the results of other relevant studies suggesting that biochemical indices are not sufficiently reliable in the nutritional

Table 5. Indices of nutritional status and levels of acute phase proteins (median) in patients who received hematopoietic stem cells from bone marrow

	X	*Y*	*Y+7*	*Y+14*	*Y+21*
ALB	3.920	3.880	3.390	3.220	3.320
RBP	3.5	4.06	1.98	2.55	2.64
PAB	21.3	25.2	12.7	17.2	16.6
TRF	196	177	134	144	157
AAT	185	181	221	242	274
AAG	80.5	83.4	147	140	133
CRP	0.39	0.31	8.03	3.99	1.82
SAA	1	1.15	13.3	3.8	7
Weight	66	65	63.3	60.8	77.5
Arm	27.4	27.6	27.5	26.5	27.7
Skinfold	16	13.5	13	11	18.5
Fat	10.2	10.3	9.5	8.95	20.7
KJ/min	4.1	3.65	2.6	3.4	3.9

For abbreviations see footnote of Table 2 assessment of HSCT patients because the levels of these substances are markedly affected by the acute phase response (measured with acute phase proteins' levels) secondary to infections, which frequently complicate transplantation [19, 24]. We found that changes in the levels of PAB and TRF can be helpful for the nutritional assessment during allogeneic HSCT. PAB level below normal range (< 17 mg/dL), measured 8 days after the end of the conditioning regimen is helpful in making a decision about starting TPN. Then, estimation of TRF is of great importance. Its level, measured 8 days after the end of the conditioning regimen and reduced more than 30% under the lower limit of normal (i.e. 168 mg/dL) can play the same role as indicator of malnutrition development. These findings can be taken as binding recommendations provided that the initial levels of PAB and TRF (before starting the conditioning regimen) are not below the normal values.

Patients' body weight loss more than 10% of its initial value is commonly known as indication for starting nutritional support with TPN [4]. We found that day y+7 is the most important time point to make a decision for TPN and 3 parameters of nutritional status can help to it: body weight, PAB and TRF.

Thus, nutritional assessment of HSCT patients using selected parameters is possible and provides very important information, which can rationalize nutritional support during HSCT.

Measurement of body fat (%), triceps skinfold thickness and REE did not help assessing the nutritional status and support during allogeneic transplantation. Similar results also come from other transplantation centers [24, 26-29].

The results of our study show that the patients' nutritional condition after peripheral blood stem cell transplantation is better than after bone marrow transplantation. Although the investigated parameters did not return to normal until the end of the study, the degree of malnutrition was greater when bone marrow was the source of hematopoietic stem cells. These results are similar to data published by other authors [22].

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