Nutritional therapy during bone marrow transplantation. An overview

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Summary

Bone marrow transplantation (BMT) is a treatment which often results in nutritional complications. Common conditions affecting dietary intake are mucosal membrane injuries, nausea, vomiting and anorexia. Dietary advice is therefore a necessary part of treatment.

The diet situation is complicated by the absence of international dietary guidelines for BMT. The dietary approach varies between hospitals. Most commonly patients receive sterile, low-microbial, modified or normal diet. In Sweden all hospitals use different diets. Based on the current literature the authors propose that a modified diet is preferable in the BMT-patients. Today there are no Nordic dietary recommendations for BMT patients. Dietitians in the Nordic countries have begun a cooperative effort to establish guidelines to standardize and improve the nutrition treatment of BMT-patients.

Introduction

Bone marrow transplantation (BMT) is a part of the treatment of haematological disorders as lymphoma, leukaemia, aplastic anaemia and thalassemia. It is also used in the treatment of breast and testicular cancer. High dose chemotherapy, sometimes in combination with total body irradiation (TBI), eradicates tumour cells and suppresses the patients own haematopoiesis before transplantation where haematopoetic stem cells are infused. The cells are obtained from a sibling or matched unrelated donor (allo- geneic transplantation), an identical twin (syngenic transplantation) or the patient himself (autologous transplantation). In an autologous transplantation the patient receives his own stem cells harvested and cryopreserved prior to the transplantation procedure. Complications include graft-versus-host-disease (GVHD), infections and relapse (1,2).

On admittance to hospital the BMT-patient receives a central venous catheter. The cytotoxic therapy (TBI and/or chemotherapy) is given daily for four or five days. One or two days later the patient is transplanted. The marrow transplant procedure is technically simple. Bone marrow is infused via the central venous catheter. Marrow cells pass through the lungs and then lodge almost exclusively in the marrow cavities. Within 2-4 weeks the donor marrow graft becomes functional, and platelets, leukocytes and red cells increase in peripheral blood. Intensive supportive care is required until marrow recovery. Patients receive prophylactics against gram negative, fungal and viral infection. The transplantation day is traditionally called day 0 (3). The entrance day at hospital is subsequently called day -7 while the day of discharge usually is day 15-20 (Figure 1). Nutritional complications are very common due to the use of cytotoxic therapy, drugs and GVHD. The conditions which directly cause these complications are mucosal membrane injuries (mucositis), nausea, vomiting and anorexia. Initially well-nourished patients may require total parenteral nutrition (TPN) during the whole period in hospital (2).

At present there are no Nordic dietary recommendations for BMT-patients. In Sweden allogeneic BMT is performed at four hospitals; Sahlgrenska University Hospital in Göteborg, Huddinge Hospital in

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Scand J Nutr/Näringsforskning 4/96

Figure 1. Treatment plan of BMT-patients.
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Stockholm, Lund University Hospital and Uppsala University Hospital. Dietary advice differs at all BMT-units in Swedish hospitals. Transplantations are expected to increase in the future. This is not only due to an improved donor register which increases the supply of matching donors but also an increased number of diagnoses where BMT is a possible treatment, for example in breast cancer.

There are limited data in the literature on nutrient intake and needs in BMT-patients. The aim of this paper is to describe the importance of a proper nutritional assessment in BMT-patients and reasons of using a modified diet in BMT-patients.

Complications and diet

Graft-versus-host-disease

The type of marrow transplantation is important in terms of intestinal and liver complications. The closer the genetic match between patient and marrow donor, the less likely is a reaction against the new marrow from the patient. This reaction is called graft-versus-host-disease and only occurs in allogeneic transplantation. Signs and symptoms usually appear between days 20-60 but can appear as early as day 7. Signs of chronic GVHD differ at all BMT-units in Swedish hospitals. Stockholms, Lund University Hospital and Huddinge Hospital, a modified diet is used.

Today BMT-units in Sweden use different recommendations to base the diet on "between-meal-foods" like soup, ice-cream and yoghurt. Addition of microbiological evaluation of food items where the method was bacterial counts. Food products were considered safe when microbiological cultures yielded less than 500 Bacillus species per gram or cubic centimetre after five days of incubation (6).

A modified diet has not been clearly defined in the literature but seems to consist of a quite normal diet with some high risk foods eliminated. The diet should be kept as normal as possible without foods well known to contain pathogens. Most often dietary restrictions concern fresh fruits and vegetables only. Fruit can be eaten if it is possible to peel. Vegetables and berries must be boiled.

Should a sterile, low microbial, modified or normal diet be used?

Today BMT units in Sweden use different types of diets. At Karolinska Hospital, Stockholm, a modified diet is used. The Karolinska Hospital only autologous transplantations are done and no dietary restrictions are imposed.

At the Department of Haematology, Sahlgrenska Hospital in Göteborg, a low-microbial diet according to Pizzo's principles have been used during the last ten years. Restrictions were, however, not based on Pizzo's evaluation of food items - the "forbidden foods" were selected by some of the doctors and the nurses on what they believed were high-microbial foods. The diet approach also differed according to treatment. Dietary recommendations were defined in four different patient categories, based on an assumed variation in immune defence with treatment; 1) Patients treated only with chemotherapy, not isolated, 2) patients treated only with chemotherapy, isolated, 3) BMT-patients, autologous transplantation, isolated and 4) BMT-patients, allogeneic transplantation, isolated.

A modified diet means less restrictions than a sterile or a low-microbial one. Therefore it gives the patient more of a choice and a greater chance of actually finding tolerable food items. Isolation combined with antibiotic treatment has been proven to reduce the number of infections. Whether a sterile or a low-microbial diet has a greater protective effect than a modified diet has not yet been clarified (6,7). Doctors at Huddinge Hospital using a modified diet, however, claim that their BMT unit does not have a higher incidence of infections than other units.

We propose, based on the current literature, that a modified diet is preferable. BMT-patients are sensitive to infections irrespective of an autologous or allogeneic transplantation and should have the same dietary restrictions even if patients with an allogeneic transplantation have an increased risk of infection. An unrestricted, normal diet should not be recommended until studies have been done to establish safety.

Dietetic approach

Cooked foods are not well tolerated in BMT-patients. A better alternative would be to base the diet on "between-meal-foods" like sandwiches, Swedish thickened fruit juice soup, ice-cream and yoghurt. Addition of energy dense nutrition supplements is also recommended. This diet corresponds to a protein- and energy dense diet referred to as a modified diet with special qualities.

A study of Gavreau-Stern et al. describes the food intake of BMT-patients. The results showed that the food best tolerated can not be based on a normal diet served from the kitchen. The best intakes were reached with an à la carte system (2). To meet the special needs of BMT-patients and to get the contamination risk as low as possible the meals should be prepared as much as possible in the ward. The modified diet with special qualities is not an easy alternative but much can be gained by not using the traditional food from the kitchen.

It is however important to remember that most BMT-patients can not meet their dietary needs even with a full-time service of chefs and nutrition staff. The patients with severe complications hardly eat anything at all. The goal of the nutrition team should always be to help, appease and to do a follow-up of nutritional problems. Food has not only a physiological but also a psychological impact. It is an important part of life that should be taken special care of in isolated patients such as BMT-patients.
Nutrient requirements

Energy and protein

Energy and protein needs are generally based on the basal metabolic rate (BMR) multiplied with an activity factor and an injury factor. The activity factor is estimated as 1.2 as the patients are slightly mobile. The injury factor was used because of the metabolic stress induced by the disease and the BMT treatment. An injury factor of 1.2 for lower range of increased metabolism for a patient of BMT was estimated by Fred Hutchinson Cancer Research Centre in March and April, 1995 at the Department of Haematology in Goteborg. Patient A, B and D participated in a partly weighed food registry during their hospital stay. Table 2 shows the average nutrient intake during each patient’s stay (patient A: 20 days, patient B: 15 days, patient D: 15 days) and the estimated needs of energy and protein.

According to the two injury factors the range of energy need for patient A-D was 10.6-15.5 MJ/day (2400-3700 kcal/day). The registered energy intakes were 5.9-7.9 MJ/day (1420-1900 kcal) per day. The food records showed that the major contributions to energy intake were sweetened beverages, 11%; bread products, 10%; milk products, 10%; parental nutrition, 27%; blood transfusions, 8% and glucose solutions, 10%. The energy balance was negative in all patients. There were some individual differences in energy distribution, but average values showed that a glutamine supply improved nitrogen utilisation. Other aspects are improved fluid balance with glutamine supplemented TPN which could be related to fewer incidents of infections and less mucositis.

In most of the studies on glutamine support the supplemented groups tended to have a higher total nitrogen intake. It has not been thoroughly investigated whether it is the glutamine supplementation or the higher nitrogen intake that is the cause of the improved nitrogen utilisation. In general, the oral glutamine supplementation might offer a protection against gastrointestinal mucositis. More studies are needed to establish the role of glutamine supplementation in nutrition support of BMT patients.

Glutamine supplemented TPN. They observed that a glutamine supply improved nitrogen utilisation. Patients in the experimental group acquired less infections and had a shorter hospital stay. A glutamine supply could indeed be favourable by improving the access of energy for the intestinal mucosa and thereby decreasing the risk of an impaired gastrointestinal barrier function.

Importance of including transfusions in nutrient calculations

There is no tradition of including transfusion products in nutrient calculations. It might be argued that transfusion products are no real food, but is there really a major difference between the protein in TPN and erythrocyte concentrates? The protein in transfusion products improves the protein balance in two ways:

1) Erythrocytes and platelets decrease the protein requirements from food, TPN or enteral nutrition (EN). By replacing red cells and platelets the endogenous production of blood cells does not require as much protein as it otherwise would have done.

2) Breakdown of the transfusion products provides amino acids which can build up new protein or serve as an energy fuel.

In a study of surgical patients by Sandstrom et al. concentrates of erythrocytes were included when protein balance was measured in postoperative surgical patients. By doing

| Table 1. Some characteristics among the patients. |
|-----------------------------------------------|
| Sex | Age | BMI | Diagnosis | Transplantation Type |
|-----------------------------------------------|
| Patient A | F | 31 | 23 | CML | allogeneic | yes |
| Patient B | F | 25 | 21 | ALL | autologous | no |
| Patient C | M | 65 | 30 | ALL | autologous | yes |
| Patient D | M | 65 | 24 | lymphoma | autologous | no |

* BMI = weight/(height)^2, TBI = Total Body Irradiation.
* CML = Chronic myelocytic leukemia.
* ALL = Acute lymphatic leukemia.

| Table 2. Energy and protein intakes compared with requirements. |
|---------------------------------------------------------------|
| Energy intake kcal/day | Energy requirements kcal/day | Protein intake g/day | Protein requirement g/day |
|------------------------|-----------------------------|---------------------|-------------------------|
| Patient A | 1860 | 2300-3500 | 85 | 100-130 |
| Patient B | 1900 | 2300-3500 | 90 | 100-130 |
| Patient D | 1420 | 2300-3500 | 70 | 110-140 |

The lower value is calculated according to the assumptions of Jeejeeboy. The higher value is calculated according to the assumptions of Aker.
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Table 3. Vitamin and mineral intake in patient A, B and D.

| Nutrient   | Retinol equivalents (μg) | Vitamin C (mg) | Vitamin E (μg) | Vitamin D (μg) | Calcium (mg) |
|------------|--------------------------|----------------|----------------|----------------|--------------|
| Average intake | 500                      | 77             | 4.5            | 3.6            | 580          |
| Recommended intakes, NNR* | 800-1000                 | 60             | 5-10           | 5-10           | 800-1000     |

*NNR-Nordic Nutrition Recommendations (20)

morbidity and mortality associated with chronic GVHD. Cortisone therapy is known to increase calcium excretion. Intake of vitamin D and calcium should at least meet national recommendations. This is to prevent an unnecessary large decrease in bone mass as lost bone mass is very difficult to regain (1). Again, this hypothesis is built on logical assumptions and further investigations are needed to clarify the connection between low intakes of vitamin D, calcium, cortisone therapy and loss of bone mass.

Vitamins and minerals

Nutrients calculations showed that patient A, B and D in the earlier mentioned case studies received a major part of their protein from the concentrates of red cells and platelets. Patient A’s intake was 36 g/day which corresponds to 41% of the total protein intake. Patient B’s intake was 24 g/day or 26%. Patient D had a high intake, 40 g/day and because of his low nutrient intake the protein from the blood products corresponded to 37%.

The transfusion samples were taken from five donors after preparation of concentrates. The figures should not be considered as very exact but give us an idea of the content. As patients A-D received 100 ml erythrocytes/day and 500 ml platelets/day during their active treatment the platelets also contributed with protein despite the relative low concentration.

Supply of parenteral and enteral nutrition

Traditionally artificial nutrient supply in this patient group is almost always by the parenteral route. An enteral alternative has not been considered possible as the BMT-patient suffer from nausea, vomiting, oral mucositis and diarrhoea. However potential advantages could be gained using an enteral alternative because the parenteral nutrition also implies clinical problems. One of the major problems is overhydration which can lead to nausea, discomfort and dilution of serum proteins. Mulder et al. compared a TPN treatment with a partly parenteral, partly enteral nutrition treatment (PPN/EN) in 22 patients. Both regimes were effective in maintaining body composition. There were no differences in number of days with vomiting. Diarrhoea decreased significantly in the PPN/EN group (17), Szeluga et al. compared TPN with an enteral programme (EN) in 57 patients. The enteral alternative was not as effective as the TPN programme in preserving the body composition but it gave less overhydration. The TPN programme gave more days with diuretics, more frequent hyperglycaemia and more catheter complications. There were no differences in haematopoetic recovery, frequency of positive blood cultures, hospital stay or survival rate but TPN costs were 2.3 times higher than EN (21).

With support of the last two studies the conclusion is drawn that TPN is not the only alternative in nutrition treatment of BMT-patients. EN may be important in protecting the BMT-patient against gut-derived septicemia. Chemotherapy induces morphological and functional changes of the intestinal mucosa. Diarrhoea is probably a result of an increasing intestinal flow and electrolyte secretion from the damaged intestine. The presence of nutrients in the intestinal tract increases the motility, blood flow and proliferation of the intestinal cells. Intestinal atrophy impairs barrier function and protection against pathogenic bacteria (17).

EN might be offered as an alternative to TPN in consultation between the patient, physician and dietitian. In the study by Szeluga 10% could not tolerate EN because of vomiting and diarrhoea (21). If even 50% of the BMT-patients could accept an enteral alternative the money saved would make it possible to financially support an improved nutrition service from ward kitchens.

Nutritional status

Nutritional status in BMT-patients can be estimated by weight, height, body composition, haemoglobin, albumin, creatinine and protein in serum. Body composition is most frequently assessed by two different methods; bioelectrical impedance and anthropometry (15,22,23). There are limitations in the number of available methods due to the isolation. This is illustrated by the case studies of the four BMT-patients whose nutrition status also was followed during their hospital stay. Four anthropometric measures of skinfold thickness were performed; triceps skinfold (TSF), biceps skinfold (BSF), suprailliac skinfold and subscapular skinfold. Patient A-D only decreased their body weight by 1.2 kg on average during the examination period. The anthropometric measures were used to calculate the body composition of the four subjects according...
to Durnin (25). The patients were all clinically overhydrated with increasing skinfold thickness. According to the four measurements that were done during the hospitalisation period the skinfold sum increased from 42 to 60 mm for patient A, 48 to 59 for patient B and 53 to 60 mm for patient D. Patient C was the only one whose skinfold thickness decreased, from 81 to 71 mm. The suprailiac and subscapular skinfold varied greatly and thereby indicated the overhydration (variation 0–9 mm). TSF was at the same level during the whole study (variation 0–2 mm) while the BSF first decreased and thereafter increased at the end (variation 0–7 mm). One might argue that the energy balance was not clearly negative but considering the fluctuating anthropometric values this indicates a weight loss disguised by the relative overhydration. This is exemplified by patient D who lost more than 4 kg in one of his last days at the hospital. Anthropometry is not a method to recommend in patients who are overhydrated. Patient A-D were actively treated which made them even more overhydrated, indicated by the anthropometric values.

Bioelectrical impedance measurements gave varying results. The within-patient variation was 9-48% but the associated body weights only varied 2-6%. There was no consistency in the results. Impedance measurement was not satisfactory in the four patients. The method is based on the use of a single frequency current. Scheltinga et al. have reported better results using multi frequency impedance. Studies in healthy individuals show an agreement in results between anthropometry and impedance (23,27). Catalano et al. did a case-control study on cancer patients undergoing no active antitumoural therapy. Impedance revealed an overhydration in the cancer patients compared to the healthy individuals. Decreasing values of resistance were shown to correlate with an increasing overhydration (26).

Inpatient A-D there was no logical decrease or increase of the impedance measurements in relation with the weight change which also was considered to indicate the overhydration. Single frequency bioelectric impedance was therefore considered not to be a suitable method for BMT-patients.

The serum parameters haemoglobin, albumin, creatinine and protein were used in the case studies as indicators of nutritional status. Haemoglobin was lower than the reference values during the whole study period. All four patients had a low value of haemoglobin because of their illness.

Serum albumin is a frequently used parameter to estimate malnutrition. It was low in all patients. Concentrates decreased two weeks after transplantation. This finding agrees with the findings of others (17). It could be explained by a transcapillary leakage which follows the cytotoxic therapy or simply reflect an acute phase response. A secondary effect is the toxic effect on the liver which might impair the capacity to produce protein. This theory combined with the relative protein deficiency could explain the low values of serum protein.

None of the methods seemed preferable in estimating changes in body composition of BMT-patients. There is a need of a new method for effective measurements. The method should be easy to use with patients in isolation. The cost is also very important. The goal is to find a method dietitians can use as routine in examining the patients’ nutrition status. Today without such a method problems arise in quality assurance of the nutritional assessment.

**Nordic dietary recommendations for BMT-patients**

Today there are no Nordic nutritional recommendations for BMT-units. Dietitians who work with BMT in Nordic countries have started a co-operative effort to develop nutritional recommendations for BMT-patients (first meeting was taken place in Göteborg on November 21 and 22, 1996). The goal of the Nordic recommendations is to standardise and improve the nutrition treatment. The guidelines in nutrition treatment should contain dietary advice during hospital stay and after discharge, recommendations of nutrition supplements and how to use them, treatment plans which also contain long term follow-up, suggestions on how to measure nutrition status, a definition of the modified diet with special needs and a motivation of reasons for using it. Finally a parenteral nutrition programme. The recommendations should also be easily implemented and insure the quality of nutritional assessment. Thereby the importance of dietary treatment actually could be shown to lower costs and better the food situation for the BMT-patient.

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