Individualized nutrition for adult allogeneic stem cell transplanted patients - effect on quality of life

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1. Introduction

1.1. Malignant blood diseases and allogeneic stem cell transplantation

Allogeneic stem cell transplantation (allo-SCT) combined with several cycles of intensive chemotherapy is the only curative treatment for acute lymphatic leukaemia (ALL), acute myeloid leukaemia (AML), chronic myeloproliferative disease (KMPS) and chronic myelogenous leukaemia (CML). Allo-SCT involves transplantation of stem cell from familiy or an unrelated donor. The aim of myeloablative allo-SCT is to destroy the cancer and to restore normal engraftment. The high doses of conditioning therapy have a cytotoxic effect on the rapidly dividing cells of the gastrointestinal tract, and manifests as mucositis. An increase in mucositis is taking place at the same time as the patients` own blood cells are disappearing from the blood stream. The symptoms are most intense at the same time as the leucocyte count has reached a nadir 5-10 days after transplantation. The lining of the gut is repaired at the same time as the blood cell count is normalized (1). The most serious complications to allo-SCT are life-threatening infections and graft-versus-host-disease (GVHD). Organs which are most affected by acute GVHD (until 100 days after allo-SCT) are the skin, gut and liver. Nausea, vomiting, reduced appetite, diahorrea, malabsorption, bowel obstruction, and abdominal pain may be signs or symptoms of acute GVHD (2). Symptoms of chronic GVHD in the gut and liver GVHD (starts about 100 days after SCT) are dry mouth due to reduced saliva production, nausea, weight loss, anorexia, diahorrea and signs of chronic liver disease (2).

1.2. Nutritional status for patient who are treated with allogeneic stem cell transplantation

Most allo-SCT patients who are treated with intensive chemotherapy often have reduced nutritional status (3). Due to the transplantation phase many patients experience a significant reduction in energy intake resulting in loss of weight (4). Loss of appetite, nausea, taste and/or smell alteration, and painful mucositis cause reduced energy intake. Reduced absorption of food substances due to mucositis caused by the conditioning regime with or without GVHD and increased energy requirement due to fever and catabolic metabolism, also reduce the body weight (4). Malnutrition is associated with increased mortality (5-7), delayed time of engraftment, increased number of infections (8) and increased length of hospital stay (7). Poor oral intake is associated with severe acute GVHD (9). Most randomized clinical trials which measure nutrition status due to allo-SCT patient have focused on different biological markers, i.e. albumin, prealbumin, retinol-binding protein and transferrin concentrations. The influence of acute-phase proteins, transcapillary leakage, cytotoxic treatment, metabolic stress and toxic effects on the liver, reduce the reliability of biological data (10-13). Most studies combine biological data with anthropometric measurements i.e. body weight, body mass index, triceps skinfold thickness and/or mid-arm circumference. However, direct comparison of the results from different studies is difficult due to methodological differences such as heterogeneous diagnoses and treatment modalities, unclear end-points and small patient samples. In addition the nutritional evaluation is often limited to a few markers which do not give a full picture of nutrition status.

1.3. Nutrition intervention for stem cell transplanted patients

Several studies have evaluated the effect of different nutrition intervention for allo-SCT patients, but there have not been found evidence-based recommendations for energy requirements, use of enteral nutrition (EN) and/or parenteral nutrition (PN). There are

insufficient data to provide a scientific basis for recommendations regarding the optimal food substances, related to mucosal injury and/or gut GVHD. Several studies have compared PN with oral intake and EN. PN is traditionally used as nutrition support to allo-SCT (4). Most transplantation units, including oslo University Hospital, Rikshospitalet, starts with PN routinely when it is impossible to eat due to mucositis (11;12;14-18). Tube feeding has been considered as not recommended due to dysphagia, abdominal pain, diarrhoea, ileus, nausea and possibility for bleeding and vomiting which may lead to tube displacement or dislodgement (19). The use of EN has increased the last 10 years. Timing of tube placement and start of feeding is crucial for successful feeding (19). Some data indicate that the tube is tolerated, but there is little data on how the tolerance is assessed (20;21). Increased subclavian vein trombosis and catheter-line infections (14), fluid overload state and hepatic dysfunction (22), delayed platelets engraftment (23) and delayed resumption of oral intake (15), have been associated with PN. Studies which compare effect of PN with EN and/or oral nutrition on nutrition status or clinical end-points, have not proved better effects of PN (11). EN seems to maintain mucosal integrity and support the gut as an important immunologic organ (24). The number of positive blood cultures are less with EN compared with PN (4). A Cochrane Review recommends EN, except for gastrointestinal failure (4). Measuring gut function is difficult because diarrhoea is common through the transplantation process and invasive procedures are not recommended due to the risk for infections and bleeding. Oral intake and EN, but not PN, influence the mucosal integrity and immunological function of the gut (24). There are no data comparing oral, EN and PN.

1.4. Quality of life of stem cell transplanted patients

Several data indicate that patients who are treated with allo-SCT experience reduced quality of life (QoL) before, during and after treatment. The cancer specific QoL form EORTC QLQ-C30 is often used to measure health-related quality of life, also among the Norwegian allo-SCT population (25). EORTC QLQ-HDC29 is a module which is developed specially for high dose chemotherapy combined with stem cell transplantation and is a supplement to EORTC QLQ-C30 (26). Factors affecting nutritional intake are often scored as problematic, e.g. fatigue, loss of appetite, nausea and global QoL (27). Patients treated with allo-SCT report poorer QoL compared with those given chemotherapy alone; and QoL is also less among those not entering remission. (28). How QoL develop 5-10 years after allo-SCT remains to be determined (29). We are not aware of studies using QoL as end-point among allo-SCT patients allocated to specific nutrition interventions.

2. Aim of the study

Allogeneic stem cell transplanted patients have reduced quality of life before, during and until one year after SCT compared with normal population. Data show that quality of life is affected by nutrition status. However, there is no consensus on the optimal nutritional management of these patients. The main aim of this study is to investigate the effects of individualized nutrition on quality of life for patients treated with allogeneic stem cell transplantation.

Main hypothesis:
Patients who receive individualized nutrition have better ”global” QoL assessed with EORTC QLQ-HDC29 three months after SCT, compared to a control group who receive routinely nutrition support.

Sub-hypotheses:
Patients who receive individualized nutrition have: i) better nutrition status, ii) decreased length of hospital stay, less episodes with fever and earlier engraftment, and iii) better main QoL scores on the scale for physical and social functions, fatique, loss of appetite, nausea/vomiting and diarrhoea three months after allogeneic SCT, compared to the control group.

3. Patients and methods

3.1. Patients

A minimum sample of 100 patiens will be included in the study. This is the result of a power calculation where a difference of 15 of global QoL is the primary end-point. All patients $\geq$ 18 year who are offered allo-SCT with myeloablative condition are invited to participate in the study about 1-3 months before commencing the treatment. The patients have to give their written informed consent to participate in the study. The patiens who enrol in the study will be randomly assigned in blocks to the intervention- or control group. The main end-point is three months after SCT. We will follow the patients throughout the first year after SCT.

3.2. Nutrition intervention

The interventions start when the patients are arriving at the hospital for SCT and consist of individualized nutrition supplement for each patient until discharge. The severity of nausea, vomiting, diarrhea and mouth soreness will be a measure of the administration route of nutrition (oral, PN and/or EN). The energy requirements will be calculated and the intake monitored. The energy intake will continuously be adjusted to the energy requirements. The patients who are able to achieve oral nutrition requirement will receive a therapeutic diet using regular foods, which is lactose-reduced and energy-enriched. The naso-jejunal tube will be inserted during the first three days after transplantation and EN will be given when oral intake discontinue, and receive EN with an additional PN if the estimated requirements by the enteral route is lower than reference values. Dislodged tubes will promptly be replaced until two times in the stomach. Tubes which dislodge for more than two times or if voluminous diarrhea appears, or the patients refuse the tube, will be nourishment by the PN route only. The patients in the intervention group will receive dietary recommendation before leaving the hospital. The patients in the control group will be nourished after established routine, first by the oral route, later PN route. Naso-jejunal tube will not be inserted and enteral nutrition will not be given.

3.3. Measurement of quality of life and nutrition status

The patients score on the EORTC QLQ-C30 form at admission, i.e. 8 days prior to SCT, then after 3 and 6 weeks and after 3, 6 and 12 months. At the same time we will measure the following markers of nutritional status: Pre-albumin, retinol, vitamins D, E and K, transferrin, gonadotrophiner, testosteron, adipokines and parameters of hemostasis. We will also record routine clinical parameters as well as anthropometry (height, weight, triceps skin-fold) and body composition using electrical bioimpedance. In addition we will use the Patient-Generated Subjective Global Assessment (PG-SGA) for that is specifically designed to assess the nutritional status among cancer patients.

4. Approvals

The study was approved by the Ethical Committee, South-East Health Region of Norway and Personvernombudet at Oslo University Hospital, Rikshospitalet.

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