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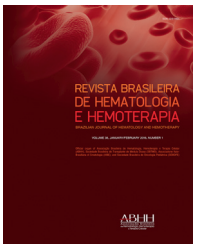

Review article

Nutritional status and hyperglycemia in the peritransplant period: a review of associations with parenteral nutrition and clinical outcomes

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ABSTRACT

Hematopoietic stem cell transplantation is an established treatment option for various hematological diseases. This therapy involves complex procedures and is associated with several systemic complications. Due to the toxic effects of the conditioning regimen used in allogeneic transplantations, patients frequently suffer from severe gastrointestinal complications and are unable to feed themselves properly. This complex clinical scenario often requires specialized nutritional support, and despite the increasing number of studies available, many questions remain regarding the best way to feed these patients. Parenteral nutrition has been traditionally indicated when the effects on gastrointestinal mucosa are significant; however, the true benefits of this type of nutrition in reducing clinical complications have been questioned. Hyperglycemia is a common consequence of parenteral nutrition that seems to be correlated to poor transplantation outcomes and a higher risk of infections. Additionally, nutrition-related pre-transplantation risk factors are being studied, such as impaired nutritional status, poorly controlled diabetes mellitus and obesity. This review aims to discuss some of these recent issues. A real case of allogeneic transplant was used to illustrate the scenario and to highlight the most important topics that motivated this literature review.

Introduction

HSCT is widely used to treat hematological and non-hematological malignancies. Compared to autologous HSCT, allogeneic HSCT (allo-HSCT) causes more severe nutritional consequences and side effects due to its more intense ablative and immunosuppressive conditioning regimen. Mucositis, nausea and vomiting, diarrhea, poor oral intake, malabsorption and prolonged malnutrition are some of the complications often observed.[1–3]

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Therefore, adequate nutritional support is paramount during all the phases of the transplant procedure,[4,5] and is an important measure for better outcomes in the short and long term.[6] Most patients need artificial nutrition at some point and for different lengths of time. Allo-HSCT patients suffering from severe gastrointestinal symptoms usually require prolonged support, frequently via parenteral nutrition (PN) because of very poor oral intake and intolerance to enteral nutrition (EN).[4–6,20] In cases of severe graft-versus-host disease (GVHD) with gastrointestinal complications, the use of PN usually becomes necessary again.[7] Nevertheless, as PN is an invasive procedure and not free of risks, its use in the quite complex scenario of allo-HSCT has been questioned.[8–10] Recent studies demonstrate that PN can actually be harmful under some circumstances, due to higher risk of hyperglycemia and blood stream infections.[11–13] In addition, despite the increasing number of studies, there is still no clear consensus regarding the benefits of EN versus PN in HSCT patients.[14]

There are several studies demonstrating the importance of a complete nutritional status assessment before the transplant.[15–17] Associations between abnormal body mass index (BMI) and non-relapse mortality (NRM) have been documented.[18–21] Correlations between pre-transplantation comorbidities and poor outcomes, especially diabetes mellitus, have also been discussed.[22]

The brief case scenario described below is used to illustrate some difficult situations that can be found in the context of HSCT. The importance of adequate nutritional support, the controversial findings in terms of the best approach and type of nutrition, and some of the deleterious consequences of PN in HSCT patients are emphasized here. Recent findings related to nutritional assessment, pre-transplantation diabetes mellitus and obesity are also reviewed.

Clinical vignette

WSA, a 27-year-old male with diagnosis of acute myeloid leukemia subtype M5 refractory to multiple chemotherapy regimens, was admitted to the Hospital de Clínicas de Porto Alegre for related mismatched allogeneic stem cell transplantation. He was obese (BMI: 30.5 kg/m^2), an active smoker, and on anti-hypertensive treatment. His performance status was ECOG 0. He received Busulfan and Cyclophosphamide plus thymoglobulin as the conditioning regimen, as well as cyclosporine and methotrexate for GVHD prophylaxis. Engraftment occurred around the third week after transplantation; it was followed by acute gastrointestinal (grade III) and hepatic (grade II) GVHD with diagnosis based on the National Institute of Health (NIH) consensus criteria.[23] This complication was refractory to first-line corticosteroid therapy (methylprednisolone 2 mg/kg) and partially responsive to basiliximab (anti-CD25 monoclonal antibody) and infliximab (anti-TNF monoclonal antibody).

An individually compounded PN was initiated on Day 5 after transplantation due to neutropenic enterocolitis with paralytic ileus and oral mucositis grade IV. The PN was calculated based on the patient's body weight of 90 kg at that time, to provide 30–35 kcal/kg/day, at least 1.5 g of protein/kg/day and a maximum of 1.0 g of lipids/kg/day. This composition corresponded to 20–25% of total calories coming from protein (10% amino acid solution), 50–60% from dextrose (50% glucose monohydrate solution) and up to 30% of total calories from lipids (20% lipid emulsion).[1] This diet was maintained for approximately three weeks because of very poor oral tolerance and no safe access for tube feeding due to thrombocytopenia. However, the PN had to be discontinued for short times during this period because of severe hyperglycemia. The patient had a medium glycemic level of around 80–120 mg/dL before starting PN. This complication, related to the use of corticosteroids and immunosuppressants, became clearly worse after the introduction of PN as his serum glucose peaked at 300–400 mg/dL. Even with a reduction of the glucose infusion rate, reduction of total caloric amount of PN to 20–25 kcal/kg/day and high doses of continuous IV insulin administration, the glycemia remained poorly controlled. The PN was interrupted. The patient refused tube feeding, so oral nutrition was initiated according to his tolerance. He had several infectious complications, such as bacterial sinusitis and pneumonia, and died from gram-negative sepsis three months after hematopoietic stem cell transplantation (HSCT).

Pre-transplantation nutritional assessment

HSCT involves an increase in nutritional and metabolic demands that is partially explained by the deleterious effects of the conditioning regimen on the gastrointestinal tract.[1] Furthermore, the occurrence of fever, infections, and the prolonged time of immunosuppression create a hypermetabolic state that can further exacerbate nutritional deficits.[5,24] It is known that an impaired nutritional status before transplantation can affect complications and clinical outcomes of HSCT, in particular allo-HSCT.[15,18,19] In malnourished patients, there is evidence of increased mortality rates, prolonged length of hospitalization and delayed time to engraftment. Moreover, the NRM is higher for the extremely underweight, overweight and obese.[21,25]

There are innumerous available nutritional assessment methods, although none are specific for the HSCT population. Screening questionnaires can be used when combined with a physical examination, biochemical markers, and anthropometry, i.e., the measurement of weight, height, skin folds and circumferences. Single methods have limitations and are inefficient.[17] Liu et al. evaluated and compared different questionnaires in patients with leukemia, and showed a better clinical applicability of the Nutritional Risk Screening 2002 questionnaire (NRS 2002) to detect malnutrition before transplantation.[26,27] The main components of the NRS 2002 are: (1) severity of primary disease and its impact on nutritional status, (2) recent changes of body weight, (3) changes in dietary intake and (4) body mass index. A NRS score $\geq$3 defines nutritional risk, information that can contribute to the planning of peritransplant nutritional support.[28]

In terms of body weight before the procedure, studies show a tendency of high BMI being correlated to higher risk of GVHD and NRM; similar risks are seen in patients with BMI below normal.[18] In addition to BMI and anthropometric measurements of body composition, Urbain et al. evaluated the benefit of using bioelectrical impedance analysis in HSCT patients.[29]

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