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Original article

Enteral versus parenteral nutritional support in allogeneic haematopoietic stem-cell transplantation

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SUMMARY

Background: Allogeneic haematopoietic stem-cell transplantation (allo-HSCT) is associated with frequent and severe malnutrition, which may contribute to transplant-related morbidity. While both enteral nutrition (EN) via a nasogastric tube and parenteral nutrition (PN) are effective, it remains unclear what is the optimal method of nutritional support.
Aims: We propose to compare the impact of EN versus PN on early outcome after allo-HSCT.
Methods: We evaluated the effect of initial nutritional support with EN versus PN on early outcome in 56 patients who required nutritional support after first allo-HSCT for haematological malignancies in our centre. Patients were offered EN but could decline and chose to be treated by PN.
Results: Twenty patients received myeloablative conditioning and 36 received reduced-intensity conditioning. Twenty-eight patients received EN and 28 received PN. Compared with PN, EN was associated with a lower median duration of fever (2 versus 5 days; $p < 0.01$), a reduced need for empirical antifungal therapy (7 versus 17 patients; $p < 0.01$), a lower rate of central venous catheter replacement (9 versus 3 patients; $p = 0.051$) and a lower rate of transfer to intensive care (2 versus 8 patients; $p = 0.036$). The early death rate (<100 days) was the same in both groups (14%).
Conclusions: Compared with PN, EN was associated with a lower risk of infection in allo-HSCT, without an increase in the incidence of graft-versus-host disease.

1. Introduction

Malnutrition is a major adverse prognostic factor for early outcome in patients undergoing allogeneic haematopoietic stem-cell transplantation (allo-HSCT).[1,2] In contrast to other factors that influence transplant-related morbidity and mortality, such as age, diagnosis and disease response status, malnutrition can be addressed easily. For this reason and given its beneficial effects, nutritional support is recommended in patients undergoing allo-HSCT[3]: further to preventing weight loss and protein–energy malnutrition.[4–7]

Compared with parenteral nutrition (PN), enteral nutrition (EN) via a nasogastric tube (NGT) appears more physiological has been shown to yield a lower incidence of complications due to infection, and to confer a survival benefit in diverse patient populations, including patients in intensive care units (ICU) and cancer patients.[8–10] Both European and American nutrition societies recommend using EN as first-line support in patients with a functional gut.[3,11–13] EN facilitates better preservation of mucosal trophicity, which is recognized as a key obstacle to bacterial translocation and subsequent systemic infection.[14]

EN has relevance for patients undergoing allo-HSCT, for whom infection is a major cause of early mortality. However, in routine clinical practice, PN is used in preference to EN: EN is considered inefficient or poorly tolerated because of digestive damage related

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to conditioning regimens, infections or graft-versus-host disease (GVHD).[15] To date, only one prospective, partially randomized study[16] has evaluated EN *versus* PN in 34 children undergoing allo-HSCT. In this study, EN was found to be well-tolerated, efficient in terms of nutritional state and yielded cost benefits. Similarly, only one nonrandomized study[17] has evaluated PN versus EN in adult patients undergoing allo-HSCT with myeloablative conditioning (MAC). In this study, EN patients were found to experience a lower incidence of acute GVHD and a lower Day +100 infection-related mortality rate than patients receiving PN or oral nutrition alone. However, a recent Cochrane Collaboration review[18] concluded that insufficient consistent data exists to assess the benefits of EN versus PN in patients undergoing allo-HSCT. Here, we propose to retrospectively evaluate the effect of initial nutritional support with EN versus PN on early outcome after allo-HSCT.

2. Patients and methods

2.1. Patients

The retrospective study reported herein was conducted in the Cell Therapy and Clinical Haematology Unit, University Hospital, Clermont-Ferrand, France. Since January 2009, the mode of initial nutritional support (EN or PN) has been selected according to patient's decision. During a pre-transplantation interview, patients are provided with comprehensive information regarding nutritional status, nutritional support and its modalities. Patients received advice on an on-going basis from a multidisciplinary team to support their decision.

Patients aged >16 years who underwent allo-HSCT between January 2009 and October 2010 and received nutritional support were eligible for inclusion. A minimum post-transplant follow-up of 100 days was required. Patients with progressive disease at transplantation, or with a history of allo-HSCT, were excluded.

2.2. Transplantation procedures

Patients received allo-HSCT according to the modalities and standard protocols of our centre, which are accredited by the Joint Accreditation Committee – ISCT (Europe) (JACIE, Certificate number: F-023-2011) and the European group for Blood and Marrow Transplantation (EBMT).[19] Patients were attended in high-efficiency particulate air filter rooms. During the allo-HSCT procedure, all patients underwent implantation of a central venous catheter (CVC) which is required for 24-h continuous infusion of such drugs as anti-microbial or immunosuppressive agents. MAC or reduced-intensity conditioning (RIC) was initiated after CVC placement. For GVHD prophylaxis, patients received initial post-transplant immunosuppressive therapy with 2 mg kg^{-1} day^{-1} cyclosporine and, in cases of pheno-identical donor, short-course methotrexate. Infection prophylaxis was administered from admission to discharge; this comprised fluconazole and oral valacyclovir. *Pneumocystis jirovecii* and toxoplasmosis prophylaxis comprised sulfamide-based treatment.

2.3. Nutritional support

Local nutritional procedures for EN and PN, defined and validated by the JACIE, have been used systematically since 2008. Nutritional support was initiated on Day +1 after transplantation. At admission, each patient underwent a clinical and biological nutritional evaluation to determine weight, body mass index (BMI), serum albumin and serum transthyretin (TTR). Oral dietary intake was evaluated two to three times weekly by an experienced dietician. Dietary advice and nutritional support were adapted to attain fixed daily energy and protein requirements of 30–35 kcal kg^{-1} day^{-1} and 1.2–1.5 g protein.kg^{-1} day^{-1}.

For EN, a 9-Fr polyurethane or silicone NGT was inserted and its position in the stomach controlled by X-ray, according to the recommendations of the National Health Authority (Haute Autorité de Santé) and the French Nutrition Society (SFNEP).[20,21] EN was delivered overnight via a pump and gradually increased over 5 days, depending on digestive tolerance. EN intake provided 50–70% of patients' total energy requirements and could increase to 100% in patients incapable of spontaneous oral intake of nutrition. EN was administered using a standard polymeric formula (1 kcal/mL; 0.04 g protein/mL) as follows: 500 mL at Day +1 and Day +2, 1000 mL at Day +3 and Day +4. The solution was switched for a hyperenergetic polymeric formula (1.5 kcal/mL; 0.06 g protein/mL) from Day +5. In cases of intolerance, additional or total PN was given.

PN was infused via a CVC overnight, for a minimal duration of 12 h; the total duration was based on the glucose flow rate, that is, <4 mg kg^{-1} mn^{-1}. Perfusion of an all-in-one standard nutritive solution (with vitamins and trace elements but without glutamine supplementation) was initiated at Day +1 to provide 50–70% of patients' energy requirements and could be increased to provide 100% in patients incapable of oral alimentation. In the all-in-one standard solutions used in our unit, lipids represent 35% of total calories and the glucose/lipid ratio is 58/42. In cases of cardiac intolerance (shortness of breath and leg swelling) or hepatic intolerance (icteric cholestasis), which limit PN increase, additional or total EN was given.

EN or PN administration was stopped when oral dietary intake approached energy and protein requirements: this generally occurred at the same time as haematopoietic recovery and usually before Day +30.

2.4. Data collection and definition of criteria

All clinical and biological data including daily complete blood count data were recorded daily by physicians. Standard protocols for managing transfusion support, infection, CVC removal, mucositis, GVHD and transfer to ICU were devised before the start of the present study and were accredited by the JACIE.[19] Fever was defined by a central temperature ≥38.3 °C (101 °F) once or ≥38 °C (100.4 °F) persisting for >1 h. This criterion is usually being applied to initiate antibiotherapy in cases of febrile neutropenia.[22] Catheter-associated bloodstream infection was defined by differential time to positivity >120 min of qualitative blood cultures performed on specimens simultaneously drawn from the CVC and a vein.[22] In the special case of coagulase-negative staphylococci, two positive samples are required. Local inflammatory signs associated with fever were also considered to be a catheter infection. In the context of allo-HSCT, all suspected catheter infection leads to its rapid removal (<12 h). The decision to treat with antifungal therapy was based on European Conference on Infections in Leukemia (ECIL3-update2009) guidelines.[23] Invasive fungal disease was defined as reported by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG).[24] Catheter removal was indicated according to our protocols in the following cases: catheter-associated bloodstream infection, evidence for clinical local inflammation signs with tunnel infection, persistence of fever for >72 h after absolute neutrophils count recovery, septic thrombosis, endocarditis, sepsis with haemodynamic instability, bloodstream infection that persists despite ≥72 h therapy with appropriate antibiotics.

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