Nutritional and metabolic support in patients undergoing bone marrow transplantation[1,2]

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ABSTRACT Bone marrow transplantation (BMT) is a sophisticated procedure consisting of the administration of high-dose chemoradiotherapy followed by intravenous infusion of hemopoietic stem cells to reestablish marrow function when bone marrow is damaged or defective. BMT is used in the treatment of solid tumors, hematologic diseases, and autoimmune disorders. Artificial nutrition, total parenteral nutrition in particular, is provided to patients undergoing BMT to minimize the nutritional consequences of both the conditioning regimens (eg, mucositis of the gastrointestinal tract) and complications resulting from the procedure (eg, graft versus host disease and venoocclusive disease of the liver). Although artificial nutrition is now recognized as the standard of care for BMT patients, defined guidelines for the use of artificial nutrition in this clinical setting are lacking. During the past 2 decades, artificial nutrition in BMT patients has moved from simple supportive care to adjunctive therapy because of the possible benefits, not strictly nutritional, of specialized nutritional intervention. Although data exist documenting the beneficial role of special nutrients, such as lipids and glutamine, in the management of BMT recipients, the results obtained to date are controversial. The reasons for this controversy may reside in the heterogeneity of the patients studied and of the study designs. This review focuses on the need to correctly identify the different patterns of BMT to achieve reproducible and reliable data, which may in turn be used to devise precise guidelines for the use of specialized artificial nutrition in BMT patients. *Am J Clin Nutr* 2002;75:183–90.

KEY WORDS Artificial nutrition, bone marrow transplantation, glutamine, fatty acids

INTRODUCTION

Bone marrow transplantation (BMT) is a sophisticated therapeutic procedure consisting of the administration of high-dose chemoradiotherapy followed by intravenous infusion of hemopoietic stem cells to reestablish marrow function in patients with damaged or defective bone marrow. The earliest report of therapeutic marrow infusion dates to 1939, when a patient received intravenous marrow from his brother to treat aplastic anemia (1). In the late 1950s, the first attempts to cure hematologic malignancy with BMT had poor results. The discovery of human leukocyte antigens (HLAs) led to the first successful allogenic bone marrow transplantation (allo-BMT) in 1968 (2, 3). The modern era of allo-BMT was based on the development of linear accelerators to achieve uniform dose rates and delivery of radiation, advances in supportive care, and the use of the immunosuppressive agents methotrexate (2, 3) and cyclosporine (4) in the prophylaxis of graft versus host disease (GVHD). Subsequently, combined efforts in laboratory and clinical science disclosed the potentials of BMT. Over the past 20 y, BMT has made curable a large variety of oncologic, hematologic, immunologic, and hereditary diseases (5) that until a few years ago had extremely poor outcomes. BMT is now a well-established therapy used to treat many diseases (**Table 1**) and administered to thousands of patients yearly (5).

TYPES OF BONE MARROW TRANSPLANTATION

At present, 2 types of BMT can be performed: allo-BMT and autologous BMT (a-BMT). In addition, in the past decade, hemopoietic stem cells collected from peripheral blood (peripheral blood progenitor cell transplantation, or PBPCT) have been increasingly used in autologous and allogenic transplantations. Cord blood stem cell transplantation (cord blood transplantation) from both related and unrelated donors has also been used recently to treat patients with hematologic disorders.

Allogenic bone marrow transplantation

Allo-BMT involves the transfer of marrow from a donor to a recipient. The best results are obtained after the transplantation of marrow from a sibling donor who is an HLA-genotypic match, but only 30% of patients have such a donor. BMT from an HLA-phenotypically identical unrelated donor or from cord blood are other options for patients who lack a donor in the family.

After the donor has been identified, the patient undergoes high-dose radiotherapy or chemotherapy or both to induce the immunosuppression necessary to avoid destruction of the allograft by residual, immunologically active cells of the host and to destroy any residual cancer cells and provide space for the new

TABLE 1
Diseases treated by bone marrow transplantation

Hematologic malignancies	Solid tumors	Other pathologic conditions
Acute myelogenous leukemia	Breast cancer	Severe aplastic anemia
Chronic myelogenous leukemia	Testicular cancer	β-Thalassemia
Acute lymphocytic leukemia	Ovarian cancer	Severe combined immunodeficiency
Chronic lymphocytic leukemia	Glioma	Autoimmune disorders
Myeloproliferative disorders	Neuroblastoma	Amyloidosis
Multiple myeloma	Small-cell lung cancer	Hereditary metabolic disorders
Non-Hodgkin lymphoma	Non-small-cell lung cancer	
Hodgkin disease		

marrow to grow. Preparative (or conditioning) regimens for allo-BMT usually consist of radiotherapy combined with the administration of alkylating agents, etoposide, and cytarabine. The major advantages of an allogenic graft include the absence of malignant cells, the potential for an immunologic anticancer effect of the graft (the graft versus tumor effect), and the ability to treat both malignant and nonmalignant diseases. The major disadvantages of allo-BMT include the difficulty of finding an appropriate HLA-matched donor and the occurrence of GVHD.

GVHD is a serious complication of allo-BMT, occurring when immunocompetent cells in the graft target antigens on the cells in the recipient. GVHD is manifested primarily as symptoms and signs involving the skin, gastrointestinal system, and liver (6). GVHD can be divided into 2 distinct clinical entities: acute GVHD, occurring within 1–3 mo after BMT, and chronic GVHD, occurring >100 d after transplantation. GVHD is usually treated by a combination of immunosuppressive drugs such as corticosteroids, cyclosporine, and methotrexate (5). Because the incidence of GVHD increases with age (7, 8), allo-BMT is largely limited to patients aged <60 y.

Autologous bone marrow transplantation

a-BMT involves the use of the patient's own marrow to reestablish hemopoietic cell function after the administration of high-dose chemotherapy. The major advantages of autologous transplantation include the ready availability of a stem cell product and the absence of GVHD, which translate into lower morbidity, mortality, and cost (5, 6, 9). The major disadvantages of a-BMT include the potential for tumor cell contamination within the graft, with a higher risk of relapse (5), and the lack of a graft versus tumor effect (9).

Peripheral blood progenitor cell transplant

PBPCT consists of autologous or allogenic infusion of hemopoietic stem cells collected from peripheral blood. The cells are collected after the administration of hemopoietic growth factors, associated or not with chemotherapy (10). Potential advantages of PBPCT over a-BMT include stem cell collection without the need for general anesthesia or repeated painful bone marrow aspirations; more rapid engraftment, particularly for platelets (11); and less tumor contamination (12). For these reasons, PBPCT can be safely performed in older patients. PBPCT has also been proposed as a possible treatment for severe intractable autoimmune diseases such as multiple sclerosis, systemic lupus erythematosus, and rheumatoid arthritis (13).

Cord blood transplantation

Cord blood transplantation consists of the infusion of hemopoietic stem cells harvested from cord and placental blood immediately after delivery. Compared with bone marrow progenitor cells, umbilical cord blood cells are phenotypically different, functionally more immature, and have a higher proliferative potential (14, 15).

At present, cord blood transplantation from HLA-matched, mismatched, or even unrelated donors is performed mainly in children, but also in adults, to treat leukemia (16, 17) and other hematologic diseases (18). The incidence and severity of GVHD appears to be less after cord blood transplantation than after BMT (18–21). Candidates for cord blood transplantation also receive conditioning regimens consisting of chemoradiotherapy; prophylaxis for GVHD is achieved with cyclosporine and corticosteroids.

COMPLICATIONS RELEVANT TO NUTRITIONAL INTERVENTION

Irrespective of the type of BMT, conditioning regimens have tremendous and deleterious consequences on the anatomical and functional integrity of the gastrointestinal tract. However, relevant differences exist in the effect on nutritional status exerted by autologous or allogenic transplantation. In fact, although candidates for a-BMT receive high-dose chemotherapy, the use of peripheral stem cells and growth factors has significantly reduced the time to engraftment, the duration of profound neutropenia (<7 d), and, consequently, the duration of neutropenic mucositis. Indeed, in these patients, sufficient oral food intake is frequent, which may significantly reduce the need for total parenteral nutrition (TPN), unless severe complications occur.

By converse, allo-BMT patients receive conditioning regimens combining high-dose chemotherapy with total-body irradiation to induce profound immunodepression. Total-body irradiation is extremely toxic, inducing severe and prolonged mucositis. In addition, the occurrence of acute GVHD 10–12 d after engraftment represents an insult of major proportions, involving primarily the gut, with abdominal pain and severe diarrhea for ≤20 d in those who do not respond to immunosuppressive therapy (6). The use of high-dose steroid drugs to manage GVHD and the use of antiviral drugs to prevent infectious complications further contribute to the onset of malnutrition. The main complications of both a-BMT and allo-BMT and their relevance in the nutritional intervention are discussed below.

Mucositis of the gastrointestinal tract

This condition represents one of the main indications for artificial nutrition in patients undergoing BMT. Within 7–10 d after chemotherapy or chemoradiotherapy, patients almost invariably develop oroesophageal mucositis and gastrointestinal toxicity (22–24). These 2 conditions may result in decreased oral intake,

nausea, vomiting, diarrhea, decreased nutrient absorption, and loss of nutrients from the gut, especially amino acids, secondary to altered transmembrane transport of nutrients. Although both the severity and the duration of gastrointestinal toxicity may differ greatly among individuals, the condition significantly affects food intake and absorption for up to 2–3 wk after BMT (22, 24, 25).

Acute graft versus host disease

Although the occurrence of acute GVHD could be regarded as a positive event, because it usually implies a graft versus leukemia effect, this is a major complication that can occur from 7–10 d to ≤3 mo after allo-BMT in 30–60% of patients (6, 26–28). When the liver is involved, severe cholestasis occurs as a result of the destruction of small bile ducts. Serum bilirubin concentrations are most commonly elevated, with concomitant impairment of other liver function. Intestinal GVHD is characterized by diarrhea with or without nausea, vomiting, abdominal pain, and occasionally ileus, and results from the destruction of the intestinal crypts. As a consequence, mild to severe gastrointestinal toxicity may develop, ranging from profuse secretory diarrhea with consequent severe nitrogen loss to mucosal ulcers with possible perforations and need for emergency surgical treatment (24).

Metabolic alterations

An overall decrease in body cell mass with no changes in body fat or lean body mass has been described in allo-BMT recipients (29). These patients show an increase in extracellular fluid and a significant decrease in intracellular fluid.

BMT has a dramatic effect on the recipient, affecting protein, energy, and micronutrient metabolism. Negative nitrogen balance is common in BMT patients (30) as a consequence of both intestinal losses with diarrhea and catabolic effects on skeletal muscle initially exerted by the underlying disease, then by conditioning regimens, and subsequently by possible BMT complications such as sepsis and GVHD (26, 31). Although data on energy expenditure after BMT are equivocal, it is generally assumed that BMT patients have increased energy needs (30, 32). Carbohydrate metabolism may be affected, with impaired glucose tolerance resulting from steroid or cyclosporine administration or the occurrence of septic complications (33). BMT may also negatively affect pancreatic β cell function (30). Abnormalities in lipid metabolism are less frequently encountered in the initial phases after BMT, although elevated serum cholesterol and triacylglycerol concentrations frequently occur in patients maintained on long-term cyclosporine therapy for chronic GVHD (34–36).

Vitamin status may be altered in BMT patients as a result of poor intake and malabsorption of both water- and lipid-soluble vitamins (37, 38). Moreover, the use of cyclophosphamide and radiation has been reported to increase the need for antioxidant vitamins such as α-tocopherol and β-carotene (30, 39, 40).

Although a certain amount of trace elements are supplied with plasma infusions in some patients, malabsorption and increased needs for bone marrow reconstitution may induce trace element deficiency (41). In particular, zinc deficiency was shown to correlate with mortality after BMT (30).

Venoocclusive disease of the liver

This serious and often fatal event may complicate both a-BMT and allo-BMT, occurring in ≈20% of cases (42–44). Venoocclusive disease (VOD) is histologically characterized by the narrowing and occlusion of hepatic venules and injury to hepa-tocytes as a result of the toxic effects of chemotherapy (45, 46). The clinical manifestations of VOD appear within 2–4 wk after high-dose conditioning regimens, more frequently during the phase of profound pancytopenia before bone marrow recovery, and include increases in serum bilirubin and transaminases, often followed by oliguria, sodium and water retention and ascites, liver failure, and hepatic encephalopathy (47).

NUTRITIONAL AND METABOLIC SUPPORT

BMT is largely used in the treatment of solid tumors and hematologic malignancies, including leukemia and lymphomas. These 2 disease states have different effects on nutritional status. In fact, patients with hematologic malignancies are usually well nourished at the time of BMT, whereas malnutrition is frequent in patients with solid tumors (48). Impaired nutritional status before transplantation is a negative prognostic factor for outcome after BMT (49). In fact, the better nourished patients have a shorter time to engraftment (50). Irrespective of nutritional status, however, nutritional support is frequently delivered routinely after BMT to prevent malnutrition secondary to either gastrointestinal toxicity related to the conditioning regimen or to increased nutrient requirements. Nutritional needs are also increased because of a stress-induced catabolic state resulting from the cytoreductive therapy, the presence of sepsis, or, in allo-BMT, GVHD (31, 51–56). Nutritional requirements may be increased to achieve optimal blood cell reconstitution (30, 57, 58).

In recent years, indications for TPN have markedly decreased in favor of enteral nutrition. However, TPN is still largely used in BMT, mainly because of the gastrointestinal sequelae associated with BMT (22–25). The gastrointestinal toxicity induced by high-dose chemotherapy precludes optimal nutrient intake and absorption (22, 23, 59). Nausea, vomiting, and oroesophageal mucositis make placement of nasogastric tubes poorly tolerated by BMT patients. Moreover, virtually all patients undergoing BMT have a central venous catheter placed, through which TPN can be safely administered, especially if a bilumen central venous catheter is used. Finally, TPN allows for better modulation of fluid, electrolyte, and macronutrient administration, which is of pivotal importance when complications occur, such as acute GVHD or VOD. For example, the onset of VOD complicated by hepatic encephalopathy may suggest the need for fluid-restricted TPN enriched with branched-chain amino acids (60). This underscores the need for personalized nutritional support for BMT patients, the composition of which may greatly change during the post-BMT period. For these reasons, controlled trials of the effects of enteral nutrition in BMT patients are, to date, still scanty (61, 62).

Energy and protein needs

Although it was shown that energy expenditure may differ between a-BMT and allo-BMT patients (63), consensus exists that energy requirements in BMT recipients may reach 130–150% of predicted basal energy expenditure (32, 50, 61, 64). Therefore, ≈126–146 kJ·kg body wt^{-1}·d^{-1} (30–35 kcal·kg body wt^{-1}·d^{-1}) is usually administered. Lipids (long-chain triacylglycerols or a mix of long-chain and medium-chain triacylglycerols) may be safely administered, providing 30–40% of nonprotein energy (61, 65). Lipids may be particularly useful in achieving the energy target if hyperglycemia develops as a consequence of steroid treatment or infection. Protein needs are also elevated and generally

TABLE 2
Aims of nutritional and metabolic support in bone marrow transplantation

Nutritional	Metanutritional
Maintenance of nutritional status	Improvement of tolerance to chemoradiotherapy
	Prevention or reduction of mucositis
	Reduction of septic complications
	Maintenance of immunocompetence
	Modulation of biological responses

satisfied by provision of 1.4–1.5 g·kg body wt^{-1}·d^{-1} of a standard amino acid solution (24, 30, 61, 66–70).

Timing of artificial nutrition support

This probably represents the less well defined aspect of nutritional intervention in BMT. TPN is often considered to be an expensive procedure and is therefore started only when it becomes necessary, ie, after severe mucositis develops, significantly affecting oral nutrient intake (22–26). This may occur variably after BMT, depending on the underlying disease, type of BMT, and conditioning regimen. Moreover, it should be emphasized that in most of the studies performed to date aimed at evaluating the effects of TPN on the outcome of BMT patients, TPN was not strictly "total," because patients were allowed oral food intake (50, 61, 65, 71, 72). In the well-known study by Weisdorf et al (65) that included both allo- and a-BMT patients, for example, parenteral nutrition was initiated before chemotherapy and irradiation and continued up to day 28 after BMT, with patients being allowed oral food intake.

In the Department of Hematology at our institution, TPN is routinely initiated on day 1 after allo-BMT and continued for 15–21 d according to intensity and duration of mucositis; oral intake is not allowed during the TPN period to minimize the risk of both gut contamination from food and diarrhea. TPN is not routinely administered to a-BMT patients unless complications occur, such as prolonged mucositis. This is consistent with the evidence that the pathologic milieu and the effect of a-BMT and allo-BMT on nutritional status may be substantially different.

Evaluation of nutritional status

Although nutritional assessment is not difficult before BMT, particularly in hematologic patients who undergo BMT in fairly good nutritional condition, evaluating the efficacy of the nutritional support is more difficult. In fact, immunologic indexes are not of great value because of the underlying disease or the chemotherapy (73–75). Biochemical indexes have been shown to not accurately reflect changes in nutritional status of BMT recipients (76), and anthropometric measurements may be influenced by fluid and electrolyte disturbances (25, 29, 77, 78).

Nitrogen balance should therefore be considered the most accurate way to perform nutritional assessment in BMT patients. Nitrogen balance is the direct expression of the imbalance existing between protein breakdown and synthesis. However, in the clinical setting of BMT patients, urine collection may be difficult, and vomiting and diarrhea may make calculations of nitrogen losses less accurate (26).

SPECIALIZED NUTRITIONAL SUPPORT

Weisdorf et al (65) first provided evidence that prophylactic, standard TPN could significantly improve the outcome of BMT patients, as shown by the 3-y survival rate of TPN-treated patients compared with those who received no nutritional support. Since then, artificial nutrition has rapidly moved from simple supportive care (mainly aimed at the maintenance of nutritional status) to adjunctive therapy because of the potential metanutritional benefits of a specialized nutritional intervention (**Table 2**).

Because artificial nutritional support is provided after BMT during the delicate phase of bone marrow engraftment and reconstitution, it is conceivable that metabolically active substrates administered during this period could influence biological responses such as time to and success of engraftment, occurrence and severity of mucositis, GVHD, and VOD. This, in turn, could affect the outcome of BMT patients. This thinking is based on the evidence that some nutritional substrates are known to interfere with certain physiologic and pathophysiologic mechanisms or otherwise protect the intestine from radiotherapy- and chemotherapy-induced mucosal injuries (79) (**Table 3**). In this respect, lipid substrates and glutamine deserve careful consideration in BMT patients.

Lipid substrates

Exogenously administered essential fatty acids may interfere with the synthesis of biological effectors of immunity and inflammation such as prostaglandins and leukotrienes (91–94) via their incorporation into cell membranes (95) and might therefore play

TABLE 3
Metanutritional effects of lipid substrates and glutamine in patients undergoing bone marrow transplantation[1]

Effect	Substrate	Comment (reference)
Reduction in the incidence of lethal acute GVHD	n−6 Fatty acids	Reported (70)
Modulation of inflammatory and immune responses	n−3 Fatty acids	Possible
Prophylaxis and modulation of GVHD	n−3 Fatty acids	Possible
Prophylaxis and modulation of VOD	n−3 Fatty acids	Possible
Prophylaxis and modulation of VOD	Glutamine	Reported (80, 81)
Prevention or reduction of gut mucositis	Glutamine	No apparent effect (71, 82, 83–90)
Prevention or reduction of oral mucositis	Glutamine	Reported (84, 87)
Improvement in nitrogen balance	Glutamine	Documented (82, 86, 89)
Reduction in septic complications	Glutamine	Documented (82, 86)
Improvement in survival	Glutamine	Reported (87)
Reduction in length of hospital stay	Glutamine	Documented (82, 86)
Reduction in need for TPN	Glutamine	Reported (71)

[1] GVHD, graft versus host disease; VOD, venoocclusive disease; TPN, total parenteral nutrition; reported, positive results reported in one or more studies by the same authors; documented, positive results reported in ≥2 studies by independent authors.

an additional role in affecting the outcome of BMT patients. We previously showed that provision of a lipid-based TPN solution is associated with a lower incidence of lethal acute GVHD in allo-BMT patients (69). The mechanisms underlying these findings could only be speculated, however. It can be hypothesized that the increased availability of arachidonic acid and of its metabolite prostaglandin E_2 (93, 94), secondary to exogenous long-chain n−6 triacylglycerols, would lead to decreased interleukin 1 and tumor necrosis factor macrophage production (96), reduced expression of major histocompatibility complex antigens (97), increased T suppressor activity (98), and decreased peripheral blood lymphocyte interleukin 2 production (99).

The recent availability in Europe of intravenous admixtures containing fish-oil-derived n−3 fatty acids has set the stage to possibly exploit the biological effects of these lipid compounds in BMT patients. Their role in modulating inflammatory and immune responses in such a clinical setting, however, has yet to be entirely explored. Some of the long-described effects of n−3 fatty acids could have a role in improving the outcome of BMT recipients, at least theoretically. n−3 Fatty acid administration was in fact shown to reduce vasoconstriction and platelet aggregation (100) and to have a profound influence on cell-cell signaling during immunologic events by inhibiting cytokine secretion and lymphocyte activation and differentiation (101–103). We therefore hypothesize that n−3 fatty acid supplementation after BMT may have a role in the prophylaxis and management of BMT-related complications such as GVHD and VOD. Clinical trials aimed at verifying this hypothesis should be undertaken.

Glutamine

The rationale for administering glutamine-supplemented nutrition to BMT patients was initially based on the concept that glutamine is a primary fuel for the enterocytes and for gut-associated lymphoid tissue (82, 104–114) and that its administration enterally or parenterally could prevent or mitigate treatment-induced gastrointestinal toxicity (115–119). Several clinical trials have been performed to evaluate the effect of glutamine administration on gastrointestinal toxicity in BMT (70, 82–90); these trials failed to show a clear preventive or curative effect of glutamine on intestinal mucositis. Note, however, that most of these studies were performed in nonhomogeneous patients undergoing either allo-BMT or a-BMT for solid tumors or hematologic malignancies, which renders the interpretation of the results rather difficult. Further studies are warranted that include homogeneous patients and evaluate the possible differences exerted by the route of administration of glutamine.

Glutamine administration after BMT was indeed shown to exert positive effects on nitrogen balance (82, 86), incidence of infectious complications (82, 85), survival (87), duration of hospital stay (82, 85), and need for TPN (70), although not univocally (70, 87, 88). Of interest is the potential for the use of glutamine in the prevention or treatment of VOD. Preliminary data suggest that glutamine infusion during BMT preserves hepatic function (80). The likely mechanism of such an action is the maintenance of hepatic glutathione concentrations, which would protect hepatocytes from the oxidant stress of high-dose conditioning regimens. Glutamine supplementation may have a beneficial role in hepatic protection from VOD both as a protective agent and as a possible treatment (81). Further studies with patients at high risk of developing VOD seem indicated to investigate this potential therapeutic role of glutamine.

CONCLUSIONS

Nutritional support is considered an integral part of the supportive care of BMT patients. TPN still represents the main tool for providing nutritional support to patients undergoing BMT, despite several attempts currently being made at different institutions to feed these patients enterally.

The aim of TPN after BMT is to prevent malnutrition secondary to the gastrointestinal toxicity and metabolic alterations induced by the aggressive conditioning regimens. TPN appears to allow easy modulation of the amount of fluid, electrolytes, and macronutrients provided, which may be necessary considering the complexity and the severity of the clinical conditions possible in the post-BMT period (eg, GVHD, sepsis, VOD, and hepatic encephalopathy). The timing of nutritional support may also be critical in determining the short-term outcome of BMT patients, although controlled data are lacking.

Potential metanutritional benefits deriving from specialized nutritional intervention have recently been proposed, and artificial nutrition has moved from simple supportive care (aimed mainly at the maintenance of nutritional status) to adjunctive therapy. The possibility that the administration of specific nutritional substrates, such as lipids and glutamine, during the delicate phase of aplasia and bone marrow reconstitution may influence outcome is an intriguing topic deserving further investigation in larger controlled clinical trials. Future studies focused on the influence of nutritional support on the outcome of BMT patients should consider patients undergoing a-BMT and allo-BMT as well as those with solid tumors and hematologic malignancies separately. The latter observation is based on the concept that both the immunologic milieu of a-BMT and allo-BMT and the effect of solid tumors and hematologic malignancies on the host's metabolism may differ substantially.

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