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ROLE OF PARENTERAL NUTRITION IN CANCER PATIENTS UNDERGOING HIGH-DOSE CHEMOTHERAPY FOLLOWED BY AUTOLOGOUS PERIPHERAL BLOOD PROGENITOR CELL TRANSPLANTATION

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High-dose chemotherapy followed by autologous bone marrow or peripheral blood progenitor cell transplantation represents a recognized option in the treatment of solid tumors and hematologic diseases. Patients receiving high-dose chemotherapy are traditionally supported with parenteral nutrition with the aim to prevent malnutrition secondary to gastrointestinal toxicity and metabolic alterations induced by the conditioning regimens. Nevertheless, well-defined guidelines for its use in this clinical setting are lacking and there are several areas of controversy.

Key words: high-dose chemotherapy, parenteral nutrition.

Introduction

Several factors contribute to malnutrition in cancer patients: anorexia, nausea-vomiting, side effects of antineoplastic agents, proinflammatory cytokines produced by the immune system and by the tumor itself, circulating tumor-derived catabolic factors, immunodepression and increased resting expenditure associated with several abnormalities in glucose, protein and lipid metabolism[1]. Glucose metabolism is abnormal in cancer patients secondary to increased whole body glucose turnover and appearance of insulin resistance. Protein and lipid metabolism are also altered. These patients present an increased whole body protein turnover and muscle proteolysis. Lipid mobilization is increased from peripheral fat stores, leading to depletion of body fatty tissue. Vitamin status may also be altered in cancer patients as a result of poor intake and malabsorption of hydrosoluble and liposoluble vitamins.

Transplanted patients were also found at risk for developing the following nutrition problems associated with high-dose chemotherapy (HDC): severe nausea, vomiting and/or diarrhea; grade III-IV mucositis; loss of body weight; poor oral intake for 2-4 weeks post transplant[2-5]. In fact, HDC induces profound changes in the integrity of the mucosal epithelia of the oral cavity, esophagus and gastrointestinal tract. As a consequence, the mucosa becomes denuded, leading to bacterial, viral or fungal invasion of the bowel wall causing ulceration, malabsorption, diarrhea and pain. Usually, parenteral nutrition (PN) is given to patients undergoing HDC to help minimize nutritional consequences of conditioning regimens as well as complications resulting from the procedure (Table 1).

Nutritional assessment and administration of PN

In order to determine the best strategies for treatment of these patients, the nutritional status must first be determined. Some experts suggest that in HDC patients the initial nutritional assessment should minimally include a body weight measurement and percentage of body weight lost[6]. Additional assessment can include assays for albumin, transtyretin and C-reactive protein[6].

A number of screening and assessment tools are currently available for use in nutritional assessment, and examples of these tools include anthropometric measurements, the prognostic nutrition index and bioelectrical impedance analysis[7-9]. The clinical and anthropometric assessment should include the measurement of height and weight, performance status, amount and rate of weight loss, a calculation of body mass index, and calculation of energy requirements. Anthropometric

Table 1 - Aims of parenteral nutrition in cancer patients treated with HDC

Minimize nutrition-related side effects
Prevent or reverse nutrient deficiencies
Allow a better modulation of fluid, electrolytes and other elements
Preserve lean body mass
Help patients better tolerate treatments
Aid in recovery and healing
Improve quality of life

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measurements should also include skin fold thickness or the mid-arm muscle circumference. Physical examination can establish the diagnosis of muscle wasting and specific nutrient deficiencies. Bioelectrical impedance analysis measures electrical resistance based on lean body mass and body fat composition. Unfortunately, the values obtained using such tools can be altered by the hydration status and comorbidity frequently found in these patients. Serum albumin and transferrin are the most common serum proteins measured. Other laboratory parameters useful in nutritional assessment include serum glucose, electrolytes, renal and hepatic function tests and a 24-h urine collection for the measurement of nitrogen balance. Nitrogen balance is the direct expression of the balance existing between protein breakdown and synthesis; however, in these patients vomiting and diarrhea may make calculations of nitrogen losses less accurate.

Most patients undergoing HDC have a central venous catheter through which PN can be safely administered, especially if a bilumen central venous catheter is used. Many premixed balanced PN bags are available commercially. The formulas contain a combination of amino acids, dextrose, lipids, vitamins and fluids. The addition of minerals, hydrosoluble and liposoluble vitamins, electrolytes and additives such as insulin and antacids completes the basic composition of the solution. PN solutions are hyperosmolar and can have a wide range of Kcal/mL. The recommended daily nonprotein calorie intake is between 25 and 35 Kcal/kg, and the recommended daily nitrogen intake is between 200 and 250 mg/kg[6]. Usually, 60-70% of total nonprotein calories should be provided as dextrose and 30-40% in the form of an intravenous fat emulsion. Central infusions are not limited by osmolarity due to use of a large vein. Patients receiving PN should be monitored regularly by measuring weight, fluid balance, serum glucose, urea, electrolytes, plasma proteins, and liver function tests.

Serious complications from PN in these patients include catheter-related infections and metabolic complications (hyperglycemia, electrolyte abnormalities, abnormalities in liver enzymes). If primary catheter sepsis is confirmed, the catheter must be removed immediately; the catheter tip should be sent to the laboratory for culture, and appropriate antibiotic therapy should be administered.

Discussion

Although PN traditionally represents an integral part of the supportive care in patients treated with HDC followed by autologous bone marrow or peripheral blood progenitor cell transplantation, the real effectiveness of this treatment remains unclear[6,10,11]. The American Society for Parenteral and Enteral Nutrition practice guidelines report that all patients undergoing HDC with myeloablative conditioning regimens are at nutrition risk and should undergo nutrition screening to identify those who require a nutrition care plan[10]. For the American Gastroenterology Association, the indications for PN in patients undergoing bone marrow transplantation are unclear, and the decision to use it or not during the time of transplantation will have to be made by the responsible physician in the absence of any clear direction from randomized controlled trials[11].

An analysis of the published trials identified by searching the Cochran Library, MEDLINE, EMBASE and CINAHL was performed by Murray *et al*.[12] to determine the efficacy of enteral nutrition (EN) or PN support in this clinical setting. The authors concluded that for the lack of assessable data the relative effectiveness of EN *versus* PN cannot be evaluated. In fact, few data exist in the literature due to a paucity of well-designed clinical trials[13-16] (Table 2).

Weisdorf *et al*.[13] randomized 137 patients to receive PN starting one week prior to transplant or hydration with a 5% dextrose solution containing electrolytes, minerals and vitamins. In the study, overall survival, time to relapse and disease-free survival were significantly improved in the PN group. Additionally, Iestra *et al*.[14] in their retrospective analysis concluded that PN is not required for all patients undergoing intensive cytotoxic therapy. It was suggested that only the screening of nutritional status at the start of therapy followed by monitoring of oral intake will allow a more appropriate identification of patients requiring PN[14].

Szeluga *et al*.[15] randomized 57 patients to receive PN *versus* an individualized EN feeding for four weeks after bone marrow transplantation[15]. EN was well tolerated, but 75% of the patients required supplemental peripheral infusions of amino acids to meet nitrogen needs. Although the enteral feeding program was less effective in maintaining body cell mass, the hematopoietic recovery rate, length of hospitalization and survival

Table 2 - Summary of randomized trials with PN in cancer patients treated with HDC

Authors	No. of patients	Aim of the study	Results
Weisdorf *et al*.[13]	137	PN *vs* hydration	OS & DFS improved in PN group
Szeluga *et al*.[15]	57	PN *vs* EN	No difference
Roberts *et al*.[16]	55	PN *vs* oral diet	Weight & anthropometrics better maintained in the PN group

OS, overall survival; DFS, disease-free survival.

did not differ between the two groups. Nutrition-related costs were 2.3 times greater in the PN group, suggesting that EN should be used if feasible.

Recently, Roberts *et al*.[16] compared total PN *versus* oral diet in 55 autologous hematopoietic cell transplant recipients. Parameters studied included length of stay, engraftment, infections, survival, weight, anthropometrics and quality of life. No significant differences were found between the two groups for any of the above parameters except weight and anthropometrics, which were better maintained in the total PN group than the oral diet group.

Timing and duration of PN has not been clearly established in this clinical setting. In clinical practice, PN is usually started when it becomes necessary, in particular when the development of severe mucositis interferes with a regular oral nutrient intake, and is continued until hematological recovery and resolution of the gastrointestinal toxicity. Some authors have suggested that PN should not be initiated until oral caloric intake is less than 50% of basal needs and serum albumin level measures less than 3 g/dL[2]. Sonis *et al*.[3] reported a mean of 8.8 days of PN in a series of 92 patients treated with HDC followed by autograft or allograft. However, according to the ASPEN guidelines, PN should be discontinued as soon as conditioning-related toxicity has been resolved after stem cell engraftment[10].

Glutamine supplementation in PN has received increased attention in the research community in recent years. Glutamine is a nonessential amino acid that plays an important role during stress and catabolic conditions, including bone marrow or peripheral blood progenitor cell transplantation. In particular, glutamine supports the function of the intestinal mucosa and is used at high rates by cells of the immune system. Studies have shown, although not univocally, that adjunctive glutamine treatment in transplanted patients may exert positive effects on nitrogen balance, incidence of infections, duration of hospital stay, survival and lymphocyte recovery[12,17-20]. In the recent study by Piccirillo *et al*.[20], glutamine-enriched PN resulted in a significant improvement of immune recovery after HDC, demonstrated by a rapid absolute lymphocyte recovery and the pattern of the lymphocyte subsets. In the study, a significant positive effect on mucositis was also documented, and the effect was dose related.

Recently, intravenous admixtures containing fish-oil-derived n-3 fatty acids have become available. Exogenously administered fish-oil-derived n-3 fatty acids, eicosapentaenoic acid (EPA) and docasahexaenoic acid, may interfere with the synthesis of biological effectors of immunity and inflammation such as prostaglandins and leukotrienes[21,22]. Studies of EPA supplementation in weight-losing patients with pancreatic cancer have demonstrated stabilization of weight loss and improvement in performance status[23]. The role of EPA supplementation in patients treated with HDC is currently being studied.

Conclusions

Artificial nutrition should be considered in patients treated with myeloablative chemotherapy with the aim to prevent malnutrition secondary to gastrointestinal toxicity and metabolic alterations induced by the conditioning regimens. In view of the reported data, there are no standard modalities even when total PN is recommended for patients with severe mucositis[6]. PN allows for a better modulation of fluid, electrolyte and other elements, which is of pivotal importance when complications occur. The possibility that PN or the administration of some nutritional elements, such as glutamine and n-3 fatty acids, may influence favorable clinical outcomes deserves further investigation. Finally, considering the common use of artificial nutrition in this clinical setting, randomized controlled trials are desirable and necessary.

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