

Artículo especial

Nutritional intervention in oncohematological patient

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Abstract

Background: Oncohematological diseases such as lymphoma or leukaemia affect an increasing number of newly diagnosed patients in Spain and other countries. Both disease and treatment may have a negatively impact in the nutritional status of the patient. Malnutrition is not uncommon among oncohematological patients. This situation can compromised the course of the disease, the clinical response of the treatment and the patient's quality of life.

Method: The implementation of a multidisciplinary approach and a systematic and protocolled nutritional assessment would be useful when dealing with haematological malignancies.

Results: We present a proposal of protocol for nutritional intervention in oncohematological patients. This proposal is been developed from the analysis of the published literature as well as clinical practice of a multidisciplinary team specialized in the management of patients with haematological malignancies.

(*Nutr Hosp.* 2012;27:669-680)

DOI:10.3305/nh.2012.27.3.5863

Key words: *Nutritional assessment. Nutritional support. Oncohematological patient. Multidisciplinary team.*

INTERVENCIÓN NUTRICIONAL EN EL PACIENTE ONCOHEMATOLÓGICO

Resumen

Objetivos: Las enfermedades oncohematológicas como el Linfoma o la Leucemia afectan a un número importante y creciente de personas en España. Tanto la enfermedad como las distintas modalidades de tratamiento que puede llegar a precisar el paciente a lo largo del curso de la misma impactan negativamente en el estado nutricional del paciente, no siendo infrecuente el desarrollo de desnutrición, situación que compromete la evolución, la respuesta al tratamiento y la calidad de vida del paciente.

Método: La implementación de una estrategia multidisciplinar, sistematizada y protocolizada de valoración nutricional puede resultar de utilidad a la hora de abordar a los pacientes con enfermedades oncohematológicas.

Resultados: Se presenta una propuesta de protocolo de evaluación y soporte nutricional en el paciente oncohematológico elaborada a partir del análisis de la literatura publicada al respecto, así como de la práctica clínica habitual de un equipo sanitario multidisciplinar especialmente implicado en el manejo de los pacientes con enfermedades oncohematológicas.

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Palabras clave: *Evaluación nutricional. Soporte nutricional. Paciente oncohematológico. Abordaje multidisciplinar.*

Introduction

Neoplastic haematological diseases affect the blood, bone marrow and lymphatic system. Of all oncohaematological diseases, lymphomas represent a type of cancer that has increased the most in Spain in recent

years, affecting more than one million people worldwide. Non-Hodgkin's lymphoma is the third fastest-growing type of cancer. The incidence of lymphoma increases by 3% per year, with the disease now representing the fifth leading cause of death from cancer. According to the U.S. National Institutes of Health, lymphomas account for 5% of all types of cancers in the United States, with Hodgkin's lymphoma accounting for only 1%. In Spain, it is estimated that the mean incidence of lymphoma is 3 new cases per 100,000 inhabitants each year. Leukaemia is the most common type of childhood cancer. More specifically, acute lymphoblastic leukaemia (ALL) represents around 30% of all neoplasms, with 3-4 cases per 100,000 children under age 15 per year. Acute myeloid leukaemia

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Recibido: 15-01-2012.

Aceptado: 11-02-2012.

(AML) is a disease affecting adults, with a mean age at diagnosis of 65 years, although it can occasionally be seen in children. This type of leukaemia represents 40% of all cases of leukaemia in the Western world. Its estimated incidence is 15 new cases per million inhabitants each year.

Malnutrition is common in cancer patients and has a negative impact on disease outcome. However, its prevalence in the specific case of onco-haematological patients has not been well established. Some studies show 27% malnutrition or nutritional risk in patients undergoing haematopoietic stem cell transplantation (HSCT).¹

Malnutrition can cause a substantial increase in morbidity and mortality in patients with onco-haematological disease. One contributing factor is the intensity of the treatment administered, including, in some cases, complex procedures such as HSCT, which entails increased metabolic stress. In addition, the side effects of treatment can lead to some degree of patient malnutrition, especially side effects relating to the gastrointestinal tract, which may reduce and/or make intake, digestion and nutrient absorption difficult. In addition to the anti-neoplastic therapy, the disease itself contributes to the state of protein-calorie malnutrition, leading to reduced quality of life, increased complications and decreased survival. This shows the need for a systematic strategy to assess nutritional status that allows adequate nutritional recommendations to be established for each type of onco-haematological patient based on clinical chemistry and anthropometric parameters, quantification of oral intake and tolerance, and treatment- and disease-associated complications that have an impact on nutritional status during disease progression.^{2,3,4}

The objectives of nutritional support in onco-haematological patients include: maintaining good nutritional status, preventing and/or treating complications associated with the drugs used or the disease itself that have an impact on nutritional support, and finally, improved quality of life for the patient. It can therefore be deduced that planning the right nutritional support for each stage of the disease has enormous benefits for patients.

Malnutrition in onco-haematological patients

Although the haematological neoplasm itself may cause increased metabolic stress and malnutrition, it is actually the treatments that the patient will need that are responsible for most of the mechanical or functional alterations that may affect the digestive tract and which will, in the end, have a negative impact on the patient's nutritional status (table I). The nutritional status will be even more severely affected if the neoplasm is more resistant to chemotherapy, sometimes requiring combinations of highly effective but

Table I
The chemotherapy agents most commonly used to treat onco-haematological diseases and associated side effects

<i>Alkylating agents</i>	<i>Anti-metabolites</i>	<i>Taxanes</i>
Busulfan		Paclitaxel
Cyclophosphamide	Hidroxicarbamide	
Procarbazine	Methotrexate*	
Thiotepa	Mercaptopurine	
Melphalan	Tioguanine	
<i>Vinca alkaloids</i>	<i>Anti-tumour antibiotics</i>	
Vinblastine*	Amsacrine	
Vincristine	Bleomycin	
Vinorelbine		
<i>Anthracyclines</i>	<i>Others</i>	
Daunorubicin	Etoposide*	
Doxorubicin*	Teniposide	
Epirubicin		
Idarubicin		

*Cytostatic agents that commonly cause mucositis.

also highly toxic treatments. The different cytotoxic agents, radiotherapy and other new drugs used in onco-haematological treatment affect not only the tumour cells but also healthy cells, especially those with a high replication rate, as is the case of lymphocytes and gastrointestinal tract cells (enterocytes, colonocytes). The effects on these cells result in major functional alterations of the digestive tract and immune system, leading to malabsorption which seriously compromises the patient's nutritional status.

Malnutrition in onco-haematological patients is often of the calorie-protein form. Malnutrition in these patients has a major impact as it may worsen or prolong the neoplastic treatment-induced immunosuppression, increasing the risk of infectious complications, the main cause of morbidity and mortality during acute neoplasm treatment.⁵

There are other inherent causes of malnutrition, such as the patients' own acquired habits or previous nutritional status (anorexia/cachexia not related to the neoplastic disease), and it is therefore essential to perform an initial nutritional assessment of the patient and to apply the most suitable, protocol-controlled and personalised nutritional support possible in each case.

Baseline nutritional status is a primary prognostic factor and we should therefore indicate early nutritional support in malnourished patients.

In patients who are to undergo HSCT, the chemotherapy/radiotherapy conditioning regimen used, haematopoietic stem cell source and possible complications appearing during treatment (sepsis, graft-versus-host disease, mucositis, etc.) will determine the increase in nutritional requirements (which are generally hard to meet), increased intestinal losses and a series of cata-

bolic effects in skeletal muscle with unfavourable consequences. As a result, a catabolic state tends to be observed in these patients, which compromises both protein and energy balance and micronutrient metabolism. This balance will often be negative due to the reduced intake associated with gastrointestinal symptoms that will make it hard to meet nutrient requirements.

Nutritional status assessment in onco-haematological patients

The primary objective of the nutritional status assessment is to identify patients with or at risk of malnutrition, either as a result of the disease itself or the required treatments. The nutritional assessment therefore makes it possible to detect those patients requiring nutritional support and adequate monitoring of such support.

Malnutrition causes changes in body composition, including loss of body fat and fat-free mass, which result in weight loss and alterations in other anthropometric parameters and/or reduced plasma proteins.⁶

For the nutritional assessment, we will consider:

- *Anthropometric data:* Weight, height and body mass index ($BMI = \text{Weight (kg)}/\text{Height}^2 \text{ (m)}$). The patient's prior BMI has prognostic implications for patients who are to undergo HSCT, prolonging the time to engraftment in patients with a $BMI < 18.5$.⁷

Weight loss over time must also be assessed. Unintentional weight loss of more than 5-10% has a major prognostic significance in cancer, especially if occurring over a very short period of time of just weeks or a few months.^{8,9} Weight loss of more than 10% in the 6 months prior to HSCT has a negative impact on the transplantation outcome.

- *Clinical chemistry parameters:* *Albumin* must be evaluated before starting onco-haematological treatment. Figures below 2.5 g/dl suggest a high risk of complications. Once treatment has started, its behaviour as an acute phase reactant and its long half-life (21 days) make use as a nutritional marker difficult. *Albumin* must be evaluated together with inflammatory parameters such as C-reactive protein (CRP). Elevated CRP levels may indicate a metabolic stress situation that results in a low plasma albumin level without showing the decrease in total body protein reserve.

*Prealbumin*¹⁰ has a shorter half-life (2-3 days), responds to nutritional therapy more quickly and correlates closely with nitrogen balance. It is therefore very useful for monitoring nutritional support.

The usefulness of *transferrin* in assessing protein behaviour in these patients is made more difficult by the frequent state of iron depletion and increased transfusion requirements.

- *Subjective global assessment (SGA):* This is a simple tool used to identify patients with or at risk of malnutrition at an early stage.¹¹ It identifies patients requiring nutritional intervention who would benefit from intensive nutritional support.^{12,13}

The SGA combines data on weight change, current dietary intake compared to the patient's usual intake, gastrointestinal symptoms over the previous two weeks, functional capacity and metabolic demands.^{14,15,16}

In the patient-generated SGA (PG-SGA) (fig. 1), the patients themselves are involved in the evaluation as they complete the first part of the questionnaire, regarding medical history, while the doctor completes the rest of the assessment, regarding clinical symptoms. This also reduces the amount of time needed to complete the assessment. It is a questionnaire that can be used in all medical environments, both with hospitalised patients and outpatients, either at appointments or the patient's home.¹⁷

Based on the result of the PG-SGA, the patient is assigned to one of the three possible groups: A (well-nourished), B (moderately malnourished or risk of malnutrition) and C (severely malnourished). It has been shown that use of this tool makes it possible to discern the rate of patients at high risk of malnutrition and to generate nutritional interventions that will, to a large extent, help minimise complications due to malnutrition, thereby having a major impact on the quality of life of these patients.¹⁸

Detecting malnutrition is the first step towards establishing the different nutritional support measures and therefore the nutritional assessment must be carried out as soon as the disease is diagnosed and repeated to monitor the nutritional status during the different phases of the disease:

- When the patient is admitted to receive chemotherapy and weekly throughout the hospital stay.
- If HSCT is required, from the start of HSCT and throughout the hospital stay. With grade D, the American Society for Parenteral and Enteral Nutrition (ASPEN) recommends carrying out the nutritional assessment prior to HSCT.¹⁹
- Following discharge from the hospital, follow-up based on patient's nutritional and functional status. This follow-up should be continued until the patient recovers an adequate nutritional status. Some studies show that a large proportion of patients do not recover their pre-treatment weight until more than a year after HSCT.²⁰

Calculation of nutritional requirements

To calculate nutritional requirements (NR), we should take into account the patient's clinical condition, type of treatment to be received (from intervention with curative intent to palliative), presence or non-

PATIENT-GENERATED SUBJECTIVE GLOBAL ASSESSMENT

Please complete the following form by giving the information requested or selecting the most appropriate option

Full name _____	Age _____ years	Date / /
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Current WEIGHT _____ kg Weight 3 months ago _____ kg
FOOD INTAKE compared to 1 month ago: <input type="checkbox"/> I am eating more <input type="checkbox"/> I am eating the same <input type="checkbox"/> I am eating less Type of food: <input type="checkbox"/> normal diet <input type="checkbox"/> little solid food <input type="checkbox"/> only liquids <input type="checkbox"/> only nutritional supplements <input type="checkbox"/> very little
DAILY ACTIVITY over the past month: <input type="checkbox"/> normal <input type="checkbox"/> less than usual <input type="checkbox"/> don't feel like doing anything <input type="checkbox"/> spend more than half the day in bed or sitting down

PROBLEMS EATING: <input type="checkbox"/> Yes <input type="checkbox"/> No If the answer is Yes, indicate wick of the following problems you have: <input type="checkbox"/> no appetite <input type="checkbox"/> nausea <input type="checkbox"/> vomiting <input type="checkbox"/> constipation <input type="checkbox"/> diarrhoea <input type="checkbox"/> smells bother me <input type="checkbox"/> things have no taste <input type="checkbox"/> funny taste <input type="checkbox"/> feel full quickly <input type="checkbox"/> problems swallowing <input type="checkbox"/> dental problems <input type="checkbox"/> pain. ¿Where _____ <input type="checkbox"/> depression <input type="checkbox"/> money problems

MANY THANKS. THE REMAINDER OF THIS FORM WILL BE COMPLETED BY YOUR DOCTOR

DISEASES: _____ _____ _____
ONCOLOGICAL TREATMENT: _____ _____
OTHER TREATMENTS: _____ _____
ALBUMIN before Oncological treatment: _____ g/dl
PREALBUMIN after oncological treatment: _____ mg/dl

PHYSICAL EXAM: Fat deficit: <input type="checkbox"/> Yes. Rating _____ <input type="checkbox"/> No Muscle deficit <input type="checkbox"/> Yes. Rating _____ <input type="checkbox"/> No Oedema and/or ascites: <input type="checkbox"/> Yes. Rating _____ <input type="checkbox"/> No Pressure sores: <input type="checkbox"/> Yes <input type="checkbox"/> No Fever: <input type="checkbox"/> Yes <input type="checkbox"/> No

DECISION-MAKING SUPPORT PLAN IN PATIENT-GENERATED SUBJECTIVE GLOBAL ASSESSMENT (modified from C. Gómez Candela and Spanish Nutrition and Cancer Advisory Group. *Intervención Nutricional en el Paciente Oncológico Adulto*. Editorial Glosa. ISBN: 84-7429-176-3. Barcelona. 2003). Taking into account the SGA form, consider or indicate the corresponding score for each of your patient's clinical categories to obtain the final assessment:

CLINICAL CATEGORY	A	B	C
Weight loss	< 5%	5-10%	> 10%
Food intake	Normal	mild-moderate decrease	severe decrease
Impediments to oral intake	No	mild-moderate	severe
Mucositis	No	mild-moderate	severe
Activity deficit	No	mild-moderate	severe
Age	≤ 65	> 65	> 65
Pressure sores	No	No	Yes
Fever/corticosteroids BMT	No	low/moderate	high
Fat deficit	NO	mild/moderate	severe
Muscle deficit	NO	mild/moderate	severe
Oedema/ascites	NO	mild/moderate	severe
Albumin (before Tx)	> 3.5	3.0-3.5	< 3.0
Prealbumin (after Tx)	> 18	15-18	< 15

FINAL ASSESSMENT **A: Well-nourished** **B: Moderately malnourished or risk of malnutrition** **C: Severely malnourished**

Fig. 1.—Patient-generated subjective global assessment.

presence of malnutrition and its type, and functional status.^{21,22}

The Harris-Benedict equation will be used to calculate calorie requirements with a stress factor of 1.3-1.5 according to the level of aggression to which the patient will be subjected. On average, this calculation tends to give 30-35 kcal/kg bodyweight/day.

The presence of metabolic stress and disease increase protein requirements to around 1.5-2 g protein/kg ideal bodyweight/day.²³

To optimise protein anabolism, it is important to adapt non-protein energy intake to the amount of protein administered. Patients with high metabolic stress require a non-protein kcal/gram of nitrogen ratio of around 100.²⁴

A moderate glucose intake (never more than 5 g/kg/day) is recommended in oncological patients with metabolic stress and insulin resistance to avoid the onset of hyperglycaemia, lithogenesis and excess CO₂ production.

Water and mineral requirements will vary based on the patient's weight and height and the underlying condition.²¹ Electrolyte, mineral and vitamin requirements will be adapted to the needs of each patient and will be monitored based on the treatment administered. Hypomagnesaemia is common in patients being treated with platinum derivatives (usual with rescue regimens in lymphoma) or ciclosporin (usual immunosuppressant in allogeneic transplantation) as are reduced zinc levels in patients undergoing HSCT.²³ Magnesium, potassium and phosphorus levels should also be monitored during HSCT to correct possible electrolyte imbalances.⁹

Nutritional considerations in onco-haematological patients

To date, most published studies regarding nutrition in onco-haematological patients have been conducted in patients undergoing HSCT.

Chemotherapy

Chemotherapy induces side effects of high metabolic stress. Adverse reactions depend on the agent used, the dose administered and individual susceptibility. However, tumour proliferative capacity and chemotherapy sensitivity will also result in a greater number of chemotherapy treatments and a greater toxic effect, known as accumulated toxicity. Most chemotherapy agents, such as alkylating agents, anti-metabolites, some vinca alkaloids, taxanes, anthracyclines or anti-tumour antibiotics, affect those cells with the fastest dividing capacity. That is why neoplastic cells and digestive tract cells (cells in the mucosa lining the digestive tract become inflamed due to damage caused by the anti-cancer agents, which is known as mucositis) will suffer from the effects of such agents most.

The intestinal mucosa suffers from oedema and bleeding due to ulceration resulting in malabsorption and gastrointestinal motility alterations. Clinical symptoms are primarily mucositis, nausea, vomiting and diarrhoea, compromising the patient's nutritional status.

Radiotherapy

Adverse reactions in patients undergoing radiotherapy will depend on the area being irradiated and the total dose administered. Therefore, patients undergoing total body irradiation (TBI) will suffer more pronounced effects, primarily nausea and vomiting.²⁵ Lesions are more intense when TBI is combined with chemotherapy or immunosuppressive treatments administered during the HSCT process.

Haematopoietic stem cell transplantation (HSCT)

HSCT is an aggressive anti-neoplastic therapeutic procedure for the digestive tract, consisting of the administration of high doses of chemotherapy and/or radiotherapy during the so-called conditioning phase followed by the infusion of haematopoietic stem cells. This procedure induces major gastrointestinal changes associated with metabolic and nutritional status deficiencies. The main symptoms that patients may experience are: long-term loss of appetite, anorexia, nausea, vomiting, dysgeusia and gastrointestinal motility disorders in the form of persistent diarrhoea. Serious digestive complications such as paralytic ileus, neutropenic colitis or typhlitis may sometimes occur. Moreover, toxicity in intestinal cells can lead to diarrhoea and malabsorption, making it hard to absorb nutrients. The presence of acute or chronic graft-versus-host disease (GVHD) may prolong the duration of gastrointestinal symptoms.

The presence and severity of HSCT complications varies according to the type of transplantation and conditioning regimen, as is the case in patients undergoing allogeneic unrelated donor transplantation.²⁰ The main causes of gastrointestinal alterations during HSCT are the direct cytotoxic effect of chemotherapy on the digestive tract cells and the prolonged myelosuppressive effect. The added presence of potentially serious complications such as acute or chronic graft-versus-host disease (GVHD) or sinusoidal obstruction syndrome (SOS, previously called hepatic veno-occlusive disease) will determine the patient's clinical outcome.

Nutritional support in onco-haematological patients

Objectives

The objectives of nutritional support for onco-haematological patients are no different from the general objectives for oncological patients,²⁶ namely:

- To prevent malnutrition and related complications.
- To improve nutritional status in previously malnourished patients.
- To improve tolerance of onco-haematological treatment and its effectiveness by allowing such treatment to be given at the established time with the necessary dose and duration.
- To improve perception of quality of life.

Indications for nutritional support

Specialised nutritional support (SNS) should be indicated in:

- a) Patients with malnutrition.
- b) Patients whose oral intake provides less than 70% of their nutritional requirements for 3 consecutive days.
- c) Patients with complications that compromise the patient's nutritional status.

Both the American Society for Parenteral and Enteral Nutrition (ASPEN)¹⁹ and the European Society (ESPEN)²⁷ agree that there is no indication for routinely starting NS in oncological patients who are to undergo radiotherapy and/or chemotherapy.

Nutritional support protocol in onco-haematological patients

In order to apply the nutritional intervention protocol to patients with haematological neoplasms, we have taken the protocol designed by the Grupo Multidisciplinar de Nutrición y Cáncer (Multidisciplinary Nutrition and Cancer Group) of the Sociedad Española de Nutrición Básica y Aplicada (Spanish Society for Basic and Applied Nutrition)⁶ as our starting point. This paper defines an algorithm that can help us make decisions regarding the nutritional support of cancer patients. This algorithm takes into account the following variables when establishing the most appropriate nutritional support for each type of patient:

- a) The first variable considered is therapeutic intent: curative or with palliative intent.
The following is advised in patients with advanced disease receiving palliative care:
 1. To give priority to the patient's own wishes regarding whether or not to improve his/her level of intake and/or nutritional status.
 2. To discuss and agree on any diet objectives with the patient and to integrate these objectives into the patient's therapeutic plan so that the two are compatible.
 3. To control the most prevalent symptoms affecting nutritional status.

4. To determine which patients have a life prognosis of less than 4 weeks. In this case, the fundamental objective of nutritional intervention is to offer the maximum possible comfort, without trying to modify the actual nutritional status.

5. To obtain the necessary assistance from psychologists and social workers to provide support to both the patient and his/her family.

There are two aspects in palliative care patients that require special attention: the level of glycaemic control and dehydration.⁵⁷

- b) The second variable considered is the patient's nutritional status via the Patient-Generated Subjective Global Assessment, which allows us to classify the patient as either well-nourished, moderately malnourished or severely malnourished.
- c) The last variable to consider is the nutritional risk of the anti-neoplastic therapy (fig. 2). Patients who are to undergo HSCT require special consideration (fig. 3).

Types of nutritional support

The nutritional treatment plan includes oral diet, nutritional supplementation and artificial nutrition when nutritional needs cannot be met any other way.

Oral diet

Various symptoms will determine oral diet needs in onco-haematological patients: anorexia, dysgeusia, nausea, vomiting, xerostomia, mucositis, etc. Dietary recommendations will be aimed at increasing the energy and protein intake of the patient's diet. These recommendations will be adapted according to the patient's symptoms.²³

Opportunistic infections are still a major cause of morbidity and mortality in immunocompromised patients. The use of low-bacteria diets may reduce the incidence of infections by decreasing exposure to bacterial agents during periods of neutropenia. Some studies have examined the role of diet and infectious risk in combination with other interventions. However, it is hard to make comparisons due to the large variability in dietary restrictions. It is necessary to conduct more studies in this area.^{19,28} Until then, the implementation of dietary restrictions when purchasing, storing, handling and preparing certain foods during periods of neutropenia is indispensable. Basic recommendations for a low-bacteria diet include:

- a) Using food hygiene and handling guidelines to prevent contamination.
- b) Avoiding the consumption of raw meat, fish or eggs.

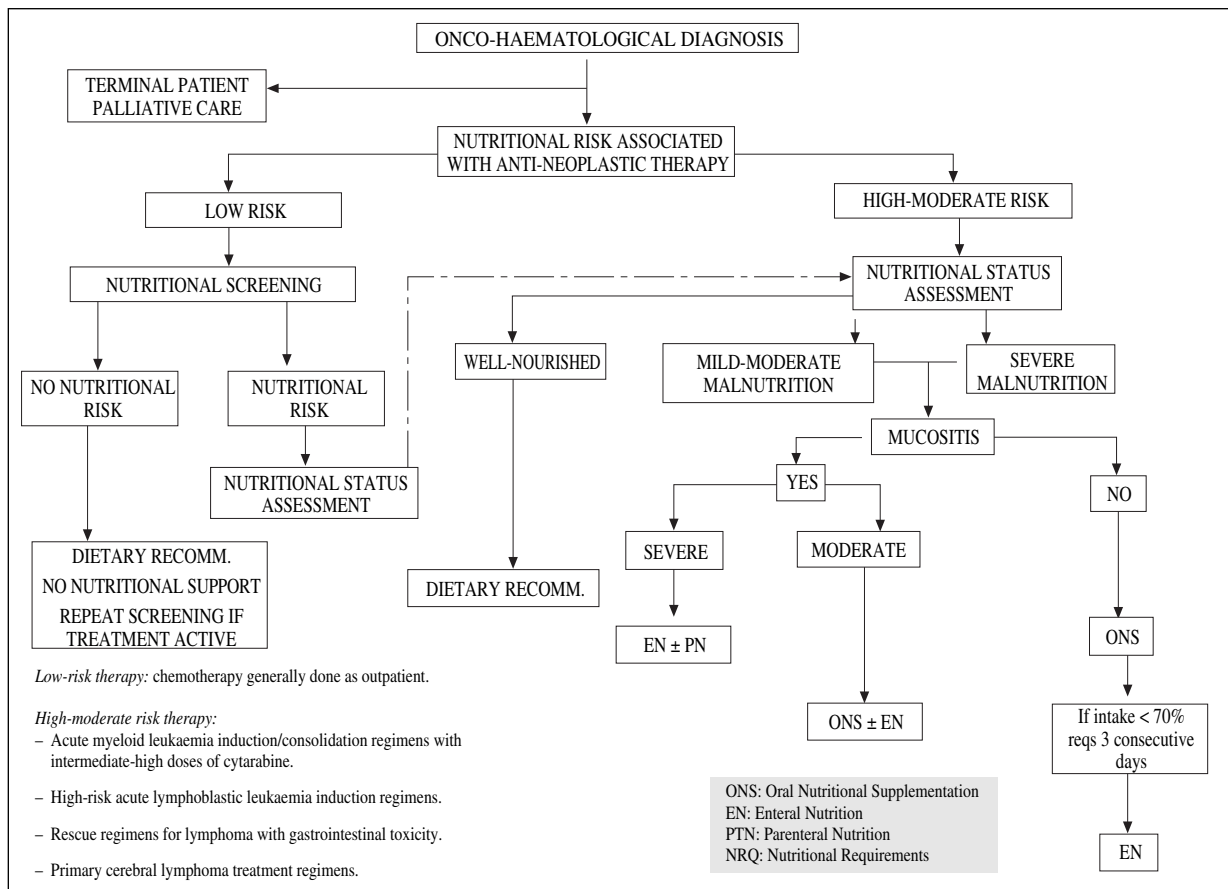


Fig. 2.—Nutritional assessment and support in onco-haematological patients.

- c) Using pasteurised, tinned and cooked food whenever possible.
- d) Avoiding raw vegetables.

Mucositis is a common complication of chemotherapy, especially in patients undergoing HSCT. According to data from the European Mucositis Advisory Group,²⁹ oral mucositis is classed as severe (grades 3 and 4) in 46% of patients during HSCT conditioning.

With severe mucositis, the presence of ulcers and other extremely painful lesions almost completely compromises the patient's oral intake, notably increasing the risk of malnutrition, dehydration and infection. The nutritional approach for mucositis must be aimed at meeting the nutritional needs of the patient by modifying the texture of the diet. Sometimes simply adapting the diet is not enough and the addition of nutritional supplementation is required.

Nutritional supplementation

Nutritional supplementation is an effective way to increase intake of macro- and micronutrients in onco-haematological patients who cannot meet their nutri-

tional needs with oral diets. Oral supplementation has proven effective at maintaining or improving the nutritional status of hospitalised onco-haematological patients, using both commercial supplements and home-made supplements using conventional foods.³⁰

Enteral nutrition

The use of enteral nutrition (EN) is indicated in malnourished patients who have a functioning gastrointestinal tract but are unable to meet their nutritional requirements by oral intake alone (ASPEN, grade C). Enteral nutrition has shown numerous advantages over parenteral nutrition in onco-haematological patients, including a reduced incidence of diarrhoea, less hyperglycaemia,³¹ less risk of severe GVHD and infections.³²

Many groups have studied the use of enteral nutrition as an alternative to parenteral nutrition in patients undergoing HSCT. Enteral nutrition generally offers numerous advantages over parenteral nutrition: it is more physiological, it has a lower cost and complication rate, more efficient use of nutrients, preservation of functional integrity, immunological benefits and a lower rate of bacterial translocation.^{32,33}

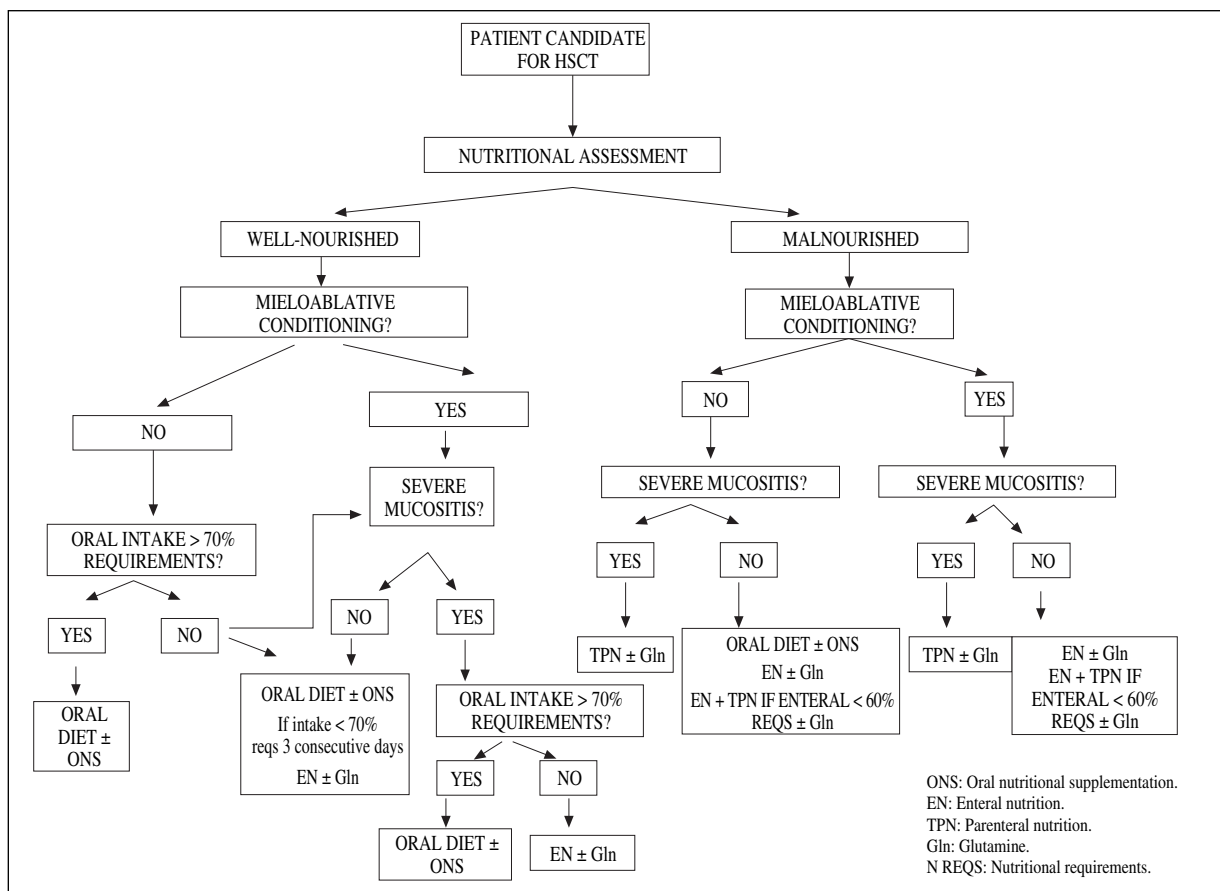


Fig. 3.—Nutritional support algorithm in patients who are candidates for haematopoietic stem cell transplantation.

However, there is a lot of controversy and great variability in its use due to the fact that its use is limited by gastrointestinal dysfunction associated with the toxicity of anti-neoplastic treatments, thrombocytopenia and neutropenia. Generally, HSCT patients are not good candidates for administration of total enteral nutrition due to nausea, vomiting, oro-oesophageal mucositis and poor tolerance of nasogastric tubes.^{28,34} Some published guidelines on enteral nutrition have demonstrated the need to supplement between 14-100% of cases with parenteral nutrition as a result of it being impossible to meet nutritional requirements by enteral route alone.^{35,36,37} Early EN is associated with better tolerance. Some studies^{32,37} have shown that insertion of the NG tube during the week of haematopoietic stem cell infusion improves enteral nutrition tolerance. During conditioning treatment, the risk of the NG tube being dislodged due to nausea and vomiting is high.

With regard to the route of administration, both nasogastric and gastrostomy tubes have been used. In some cases, the tube has been inserted prior to the transplant to avoid the risk associated with inserting the tube when mucositis is already present due to the friability of the tissue. Nasogastric tube placement is considered safe provided that mucositis is grade 2 or

less. A minimum count of $0.5-1 \times 10^9/l$ neutrophils and $10-20 \times 10^9/l$ platelets is also required.^{33,34} Nevertheless, it is recommended that the haematologist in charge be consulted to evaluate the risk of bleeding.

The use of low-osmolality, polymeric enteral formulas as a continuous infusion are generally well tolerated. Some authors³² recommend gradually increasing the infusion rate as tolerated by the patient or changing to a high-energy formula until the patient's nutritional needs are met in about one week. Regarding the use of specific nutrients, ESPEN gives a grade C recommendation with regard to the use of formulas rich in omega 3, alleging that there are no conclusive data to routinely support this recommendation in cancer patients.²⁷

ESPEN does not recommend the use of routine enteral nutrition in HSCT patients (grade C), indicating that parenteral nutrition would be preferable in patients with an increased risk of haemorrhage or infection and in immunocompromised or thrombocytopenic patients.²⁷

Despite this, there are authors who support enteral nutrition being considered a valid option in this type of patient, especially when scheduled prior to the onset of mucositis.^{32,33,38} Lipkin et al. reviewed the characteristics of HSCT patients who are candidates for enteral nutrition (table II).

Table II
Characteristics of patients who are candidates for enteral nutrition during haematopoietic stem cell transplantation

<i>Conditioning regimen</i>	<ul style="list-style-type: none"> • Reduced intensity. • Myeloablative with low gastrointestinal toxicity profile.
<i>Type of transplant</i>	HLA-matched related donor.
<i>Critical patient</i>	Trophic enteral nutrition or total enteral nutrition if the digestive tract is still functional.
<i>Prolonged recovery</i>	Problems with parenteral-to-oral transition after resolving toxicity from chemotherapy. Patient malnourished or with high risk of malnutrition.
<i>Access devices</i>	Pre-established access. Limited central venous access devices. Patient's consent to insert tube.

Adapted from Lipkin A et al., 2005.

Parenteral nutrition

The route of administration, whether central or peripheral, will depend on the planned duration of nutritional support. However, like non-oncological patients, it is common for onco-haematological patients, especially if undergoing HSCT, to be fitted with a long-term central line for chemotherapy (generally a Hickman line), which we can use for the administration of parenteral nutrition.

With regard to indications for TPN in HSCT patients, the European Guidelines on Enteral and Parenteral Nutrition (ESPEN) specifically recommend (Grade B) that it should be reserved for patients with ileus, severe mucositis and intractable vomiting and should not be routinely administered. To conclude, the use of TPN is proposed in those patients meeting criteria for malnutrition or a major risk of malnutrition and in patients in whom digestive toxicity is expected to continue being a limiting factor for oral or enteral intake.²⁸ Gastrointestinal toxicity is therefore the limiting factor for oral intake and the main indication for parenteral nutrition. Such toxicity is variable depending on the agent used. However, toxicity-dependent indications for parenteral nutrition may be modified in the future with the development of effective gastro-protective therapies. There is already a large number of drugs being studied for this purpose, including interleukin 11, sucralfate, amifostine and keratinocyte growth factor.

The best time to start TPN is unclear.³⁸ At some hospitals, this type of treatment is part of routine clinical care for HSCT and its start is determined by a set schedule. At La Paz University Hospital, parenteral nutritional support is started according to protocol on day +2 of HSCT, unless the patient is already showing signs of limited oral intake or elevated digestive toxicity prior to HSCT, in which case parenteral nutrition will be started earlier.³⁹ At Hospital Vall d'Hebron and Instituto Catalán de Oncología, TPN is only started if oral and/or enteral feeding fails.

In terms of specific nutrients in the TPN formula of HSCT patients, glutamine and different types of lipid emulsions have been studied.⁴⁰ The provision of micro- and macronutrients has been specifically covered in the calculation of requirements section, although it is worth highlighting that HSCT imposes high levels of stress that will have to be considered when calculating requirements.

European Guidelines recommend gradually discontinuing TPN when the patient can meet 50% of his/her needs by oral intake (grade C).³⁸

Specific nutrients

Glutamine

Glutamine is a non-essential amino acid that may be conditionally essential in patients in hypercatabolic states. It helps maintain the integrity of the intestinal mucosa by reducing intestinal atrophy and can improve weakened immune function in onco-haematological patients.

Glutamine plays an important role in nitrogen transport and as a precursor for nucleotide synthesis. Although several studies^{44,46,47} have evaluated the effect of enteral or parenteral administration of glutamine on gastrointestinal toxicity, none have shown a clear preventative or therapeutic effect on intestinal mucositis.

On the other hand, prospective studies suggest positive effects of glutamine on length of hospital stay, nitrogen balance, infectious complications, early HSCT-related mortality and incidence of GVHD.^{41,42,43}

In the literature, we found different studies, systematic reviews and meta-analyses with contradictory conclusions and recommendations. The latest review of Cochrane⁴⁴ shows no clinically beneficial effects in the use of parenteral glutamine in HSCT patients, but both the ASPEN¹⁹ and ESPEN guidelines³⁸ conclude that parenteral glutamine has a beneficial effect in

patients undergoing HSCT. The immense variability of the studies used and the different interpretations of such studies make it hard to reach definitive conclusions. Some studies show benefits in terms of infections,^{42,45} length of hospital stay^{41,45,46} or short-term mortality⁴² while others show contradictory results or insignificant differences.^{47,48}

ASPEN has recently published an exhaustive review of the use of glutamine in parenteral nutrition⁴⁹ and concludes that there is a trend towards fewer positive blood cultures with the use of parenteral glutamine in HSCT patients receiving TPN. However, it warns that the potential beneficial effect of glutamine supplementation remains unclear since there is only a reduced length of hospital stay in studies combining autologous and allogeneic transplants while no advantages have been shown when given post-transplant to those solely undergoing autologous transplantation. Finally, it concludes that glutamine supplementation should be further investigated in the areas of timing, dosing and cost-benefit analysis. In the review conducted by Martin-Salces et al., the recommended dose is up to 0.5-0.7 g/kg/day²² in HSCT patients.

Therefore, well-designed studies are needed to assess the potential benefits of glutamine in HSCT patients that evaluate the best time to start glutamine supplementation (pre-transplant vs. post-transplant), route of administration (oral/enteral vs. parenteral), duration of supplementation and medium to long-term effects (relapses, GVHD, SOS). The cost-benefit analysis of glutamine supplementation should also be evaluated.

Probiotics

The use of probiotics to treat diarrhoea in onco-haematological patients is controversial, despite theoretical potential benefits. At present, their use in such patients is not advised due to their immunodeficiency, risk of colonisation and bacteraemia.³³

Lipid emulsions

Soybean oil-derived lipid emulsions are rich in polyunsaturated fatty acids and are more susceptible to oxidation, which could potentially affect immune system function. The effect on oxidative stress and plasma lipid profile in HSCT patients of several lipid emulsions with a higher or lower long-chain triglyceride (LCT) content has been compared with oleic acid-enriched emulsions.⁵⁰ Oleic acid-enriched emulsions have shown a smaller increase in oxidative stress as a result of decreased lipid peroxidation and lower plasma lipid profile alterations. They should therefore be considered in TPN for HSCT patients.

The effect of the different lipid emulsions on evolutionary parameters in HSCT patients (time to engraft-

ment, hospital stay, infections, etc.) has yet to be investigated.

Nutritional support in complications of HSCT

Graft-versus-host disease (GVHD)

GVHD is a complication of allogenic HSCT that occurs when immunocompetent cells in the graft detect antigens in the recipient's cells. It can be acute or chronic. In its acute form, it primarily affects the skin, liver and gastrointestinal tract. Intestinal GVHD is characterised fundamentally by varying degrees of mucositis associated with diarrhoea with or without nausea, vomiting, abdominal pain and occasionally ileus. It results from the destruction of the intestinal crypts, with gastrointestinal toxicity developing, ranging from profuse secretory diarrhoea with consequent severe faecal nitrogen loss to mucosal ulcers with possible perforations and need for emergency surgical treatment. Skin involvement leads to erythroderma, which usually appears on the cheeks, trunk, soles of the feet, palms and the retroauricular region. When the liver is affected, severe cholestasis appears as a result of the destruction of small bile ducts.

Chronic GVHD consists of the onset of signs and symptoms after post-transplant day 100, fundamentally recurrent infections, associated immune diseases and cutaneous-mucosal, eye, gastrointestinal, hepatic and pulmonary conditions, among others. Gastrointestinal involvement affects 16% to 25% of patients, with signs and symptoms appearing secondary to oesophageal motility disorders, dysphagia and odynophagia, nausea, vomiting, abdominal pain and diarrhoea, resulting in weight loss. Treatment consists of steroids and immunosuppressants together with support, depending on the organ affected.

Nutritional support of severe acute GVHD is still under debate. Some studies suggest that limited oral intake may be associated with an increased risk of severe acute GVHD following HSCT.⁵¹ The diarrhoea that occurs during GVHD is multifactorial and includes secretory dysfunction, although osmotic factors and rapid passage are also involved. Classically nothing by mouth and TPN were recommended to reduce stool volume and improve pain in patients suffering from post-prandial pain. However, this approach results in intestinal mucosal atrophy and dysfunction, potentially leading to bacterial translocation and difficulty restarting oral feeding. Various studies have shown that enteral nutrition is safe using hypo-osmolar diets, without exacerbating digestive symptoms of GVHD.⁵² Nevertheless, it is not uncommon for patients with very high stool volume to need intravenous nutrient replacement due to the high intestinal losses and the fact that it is impossible to meet nutritional requirements via the gastrointestinal tract. It should be considered that certain risks may be associated with TPN, such as hyperglyca-

emia, hepatic impairment and an increased risk of TPN-associated infection.^{23,31} Therefore, the most suitable nutritional approach probably includes maintaining the digestive tract with a low-residue and low-lactose oral diet or a hypo-osmolar enteral diet, assessing the need for complementary TPN on an individual basis.

However, when the state of malnutrition is maintained for long periods of time, as is the case in HSCT patients, the use of nutritional support exclusively in the form of TPN is associated with atrophy of the intestinal mucosal villi and their immune function, promoting bacterial translocation and endotoxin absorption, both of which are involved in the development and maintenance of sepsis and multiple organ failure.

As a result, assessment of the nutritional status and optimal support are essential for maintaining the nutritional status of the patient during HSCT.

Sinusoidal obstruction syndrome (SOS)

Sinusoidal obstruction syndrome, formerly known as hepatic veno-occlusive disease, is a serious complication of HSCT in which the sinusoidal epithelial cells are damaged during the conditioning regimen.⁵³ Mortality may be up to 25% of cases.⁵⁴ The damaged epithelial cells may slough, causing congestion and obstruction of blood flow through the hepatic sinusoid. SOS is characterised by hepatomegaly, fluid retention, ascites and jaundice.

Patients with SOS often require parenteral nutritional support. The parenteral nutrition formula will be determined by the need to restrict fluids and specifically sodium. Furthermore, given the extreme liver impairment and cholestasis associated with the condition, manganese should be restricted to avoid accumulation of this element and associated neurotoxicity. Lipid emulsions should be adjusted due to hepatopathy and a high frequency of hypertriglyceridemia.

Some authors suggest that glutamine infusion may act as a liver protector, reducing the oxidative stress associated with conditioning treatments, and may therefore prevent the onset of SOS.⁵⁵

Conclusions

The objective of this paper is to establish a protocol for the nutritional treatment of onco-haematological patients with the hope that this may result in an improved efficacy and tolerance of treatments and an improved quality of life for patients during oncological treatment.^{56,57}

Acknowledgements

We would like to thank Nestlé HealthCare Nutrition S.A. for its support and for enabling us to meet on several

occasions to undertake this study. However, Nestlé HealthCare Nutrition S.A. has not been involved in any way in the editing or publication of this article.

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