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Nutrition treatment does not improve the efficacy of oncological treatment

Aleksandra Kapała

A beneficial effect of nutrition treatment on multiple aspects of oncological therapy is chiefly demonstrated by preventing and in treating the wasting syndrome and cancer cachexia accompanying the cancer disease. The presence of the wasting syndrome prior to commencing treatment is associated with shorter time for developing complications along with a shorter overall survival (OS), worse response to oncological treatment, deteriorating quality of life, poorer general status; moreover, cachexia strongly affects treatment tolerance. Clinical nutrition is one of the most significant pillars supporting oncological treatment, nonetheless, one has to be mindful of certain cases where nutritional intervention, especially parenteral nutrition, does not bring benefits, and may even be harmful to the patient. Such cases include: PN (parenteral nutrition) for patients with normal body mass and a correctly functioning gastrointestinal tract; PN due to hypoalbuminemia, in patients where feeding via the gastrointestinal tract is possible (orally or enterally); lack of refeeding syndrome prevention for cachectic patients starting PN or EN; use of feeding mixtures containing only soya oil as the sole fatty nutrient; incomplete nutrition (macronutrients or micronutrients only); inclusion of PN in patients in the terminal phase of cancer undergoing persistent nutrition therapy.

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Introduction

The protocol for conducting clinical nutrition with patients suffering from cancer is detailed in the EU guidelines of 2016 [1], as well as in the Polish guidelines of 2015 [2]. A beneficial effect of nutrition treatment on multiple aspects of oncological therapy is shown mainly by preventing and treating the wasting syndrome and cancer cachexia accompanying the tumour disease. The presence of the wasting syndrome prior to commencing treatment is associated with a shorter time to developing complications, with shorter overall survival (OS), worse response to oncological treatment, deteriorating quality of life, poorer general fitness; moreover, cachexia strongly affects treatment tolerance [3–9]. The status of clinical nutrition as a fully eligible method of aiding treatment in clinical oncology is now undisputable. Nutritional intervention may reduce surgical complications and the healing rates of wounds and mucosal reactions; it reduces infection rates and also treatment toxicity, it improves patients' general fitness and life quality, shortens hospitalisation time and diminishes treatment costs [10]. Nutritional preparation often helps a patient to start oncological therapy in the first place, or facilitates its continuation.

However, despite the indisputable benefits of clinical nutrition for oncological patients, there are cases where nutrition intervention not only fails to improve a patient's general condition, but may even worsen it. This article is devoted to situations in oncology where one should refrain from feeding; it also pinpoints frequent practical errors likely to entail serious consequences.

Applying parenteral nutrition to non-cachectic patients with a correctly functioning gastrointestinal tract, i.e. for whom PN should not be used

Parenteral nutrition has been used since the 70s of the last century. Initially, the success achieved with this

Department of Clinical Nutrition, Head and Neck Cancer Clinic, Maria Skłodowska-Curie Cancer Center and Institute of Oncology, Warszawa, Poland

treatment method for patients undergoing surgical treatment and cachectic patients have led to the attempts in using parenteral nutrition for cancer patients to prevent radiotherapy complications; especially post-radiation inflammation of the mucous membranes [10]. Efforts were also made to administer parenteral nutrition to patients with a correct body mass and a correctly functioning gastrointestinal tract undergoing oncological treatment, in order to decrease treatment toxicity and enhance treatment outcomes. 109 randomised studies and 4,000 patients were analysed in a literature review by Koretz et al. [11] which did not demonstrate any advantages in using parenteral nutrition. The potential harm, of increased infection rates in those undergoing PN, was however noticed. There was no beneficial effect on treating the complications arising from radio- and chemotherapy whenever PN was used. Current ESPEN guidelines underline that a nutritional intervention should be carried out in the first place through the gastrointestinal tract (orally, intragastrically by tube or gastrostomy, or enterally — by tube or jejunostomy). When neither of these methods can be used, and if the gastrointestinal tract cannot be accessed, (e.g. due to an obstruction), only then can nutritional intervention be applied via the intravenous route (the peripheral or central route). This recommendation is substantiated by an understanding of the pathophysiological changes occurring in the gastrointestinal tract if feeding is via the intravenous route. The basic phenomena include:

— Atrophy of villi, decreased blood flow rate in villi, lower hormone secretion of the gastrointestinal tract and absorption of nutrients;
— Damage to the natural protective barrier: smaller production of mucus and IgA;
— Changes to the intestinal flora, bacterial translocation and increasing permeability of the mucosal barrier;
— Lower secretion of digestive juices;
— Slowed peristalsis;
— Damaged liver, steatohepatitis, incorrect rotation of bile salts acids;
— Adverse changes in the function of lymphocytes B and T, macrophages and in the efficiency of chemotaxis and phagocytosis.

Considering the above, the ESPEN recommends if possible, to combine parenteral and enteral feeding. It is thought that even trophic feeding (minimum enteral feeding, delivering below 400 kcal per day) already has a beneficial effect on the pathophysiological changes described above.

It is the most often requested clinical practice to administer PN for patients with hypoalbuminemia. However, even if a hypoalbuminemia patient is cachectic, but the gastrointestinal tract works efficiently and an oral or enteral intervention is possible, it is a mistake to administer PN for such a patient. Hypoalbuminemia in oncology is, first of all, a sign of a tumour disease's activity, of cachexia and of the accompanying inflammation as well as a sign that the production of liver-produced proteins has been distorted to acute phase proteins. There are then no sufficient substrates for albumin production and concentrations of this protein fall dramatically. Unfortunately, PN will not compensate for this disorder. Effective causal oncological therapy will only improve this parameter.

Prevention of the refeeding syndrome (RF), i.e. less is more

Another common situation in clinical practice is that appropriate prevention of the refeeding syndrome is lacking; a potentially fatal complication of not only parenteral, but also enteral feeding. A mortality rate for a developed RF reaches 50%. The RF is a syndrome of severe metabolic disorders related to a critical deficiency of phosphates, potassium, magnesium and thiamine. The RF can also be referred to as a metabolic syndrome, because the shortage of phosphates prevents the activity of the ATPase, a pump necessary for producing energy for the transformation of macronutrients; mainly hydrocarbons. A consequence of the metabolic syndrome is metabolic acidosis, a shift in the haemoglobin dissociation curve to the left, cell lysis, and consequently, a rapidly evolving failure of all the systems and organs essential for living together with impaired consciousness. Exposed to RF development are those patients subject to protracted starvation and cachectic patients, i.e. such as is often seen in cancer patients. If parenteral nutrition is recommended for a cachectic patient, a calorie supply of < 50% of the calculated demand should always be started with, (usually 5–10 kcal/kg of the current body mass), and then built up gradually by increasing calories from 100 to 250 every 3 days [13–17]. Additional doses of thiamine, phosphates and vitamins dissolved in water are used in the first days of nutrition. Sometimes, in the first day, liquids and micronutrients are only given to balance out water-electrolyte abnormalities and PN is started on the second or third day. In case of enteral nutrition for extremely cachectic and long starving patients, a < 50% of the protein-energy demand is also begun with; isocaloric or peptide diets are willingly accepted, and some of the micronutrients are supplemented via the intravenous route. It should be kept in mind that the best RF treatment method is prevention. Practically, for a cachectic patient with the body weight of 40 kg, an initial supply of protein and energy should be between 200 and 400 kcal and should gradually increase every 2–3 days to the target values depending on treatment tolerance. Most hospitals do not possess a nutrition laboratory, and only have ready-made 3-chamber bags with the calorific value substantially exceeding the above values. The number of calories supplied in such cases should be adjusted to the demand (a part of the bag to be applied).

Selection of fatty nutrients, i.e. not only is protein important

Since the onset of adopting clinical nutrition, focus has been laid on proteins — as being the nutrient dictating the renewal of tissues and cells in a body under starvation. Regardless of the above, a fatty component is also important and the current ESPEN recommendations say that fats are to cover 50% of calories from non-protein energy in a cancer patient's daily energy demand. The selection of a fatty component is also essential [18]. The first fat used in parenteral nutrition was soya oil, rich in long chain fatty acids (LCT), including unsaturated fatty acids of the omega-6 group. In the light of modern knowledge it is known that omega-6 acids interfere with the cyclooxygenase cycle and promote the production of proinflammatory and prothrombotic cytokines such as series-2 prostanoids, series-2 thromboxan and series-4 leukotrienes. There are concerns that promotion of systemic inflammation may support an inflammatory micro-environment, which facilitates cancer cell growth. In particular this happens by increased production of hypoxia induced factors (HIF). The hypoxia environment strengthens angiogenesis on the other hand, and the formation of new blood vessels allows the tumour to obtain nutrients, oxygen, which conditions its growth, survival and, consequently, enables potential metastasis [19]. It was additionally shown that nutrition based on soya only extends the hospitalisation time by 1.6 day per each 100 g of soya oil [20]. For this reason, it is a mistake to use mixtures only containing soya oil. Bags are currently commercially available containing medium chain triglycerides (MCT), olive oil rich in group n-9 fatty acids and unsaturated fatty acids of the omega-3 group [20]. All the aforementioned fatty components are important for a patient suffering from cancer. Soya oil should not be used as the only fatty component, however, it cannot be totally eliminated. MCT-type acids are a unique component absorbed directly to the blood system and consumed by the liver as a source of energy. Unlike LCT, they do not require the digestion of lipases, and are not transported by lymphatic routes. They are more readily available as a source for energy production than LCT acids. It is important that MCT acids exhibit a protein saving effect. Beta-hydroxybutyrate acid and acetoacetic acid, being a fuel for mitochondria instead of glucoses, are produced from them. Hence, by substituting glucoses, they limit gluconeogenesis from the body's own proteins [21]. All these MCT metabolic distinctions are especially vital for cachectic patients and allow for faster energy gain. Unsaturated fatty acids of the omega-3 group exhibit anti-inflammatory action, interfere with the cyclooxygenase cycle and promote the production of cytokines with a smaller inflammatory potential, namely series-3 prostanoids, series-3 thromboxan and series-5 leukotrienes. As a fatty nutrient in parenteral and enteral feeding, they are recommended for surgery patients irrespective of the body mass in case of surgery of the upper section of the gastrointestinal tract and head and neck, and also for malnourished patients intended for extensive abdominal cavity procedures. They are also recommended for the acute respiratory distress syndrome (ARDS), and for liver insufficiency. The last two cases may represent severe complications of oncological therapy. Nonetheless, olive oil containing neutral n-9 fatty acids has a neutral effect on the inflammatory process; it neither fuels it, as do omega-6 acids, nor diminishes it, as do omega-3 acids. In current clinical practice, bags containing LCT and olive oil are proposed for undernourished, non-surgery patients, especially in palliative care.

Incomplete nutrition, i.e. how to make one's own action ineffective

One of the key parenteral nutrition principles in oncology is the principle of nutrition completeness, meaning that a feeding mixture has to contain macronutrients: protein, hydrocarbons, fats, and also micronutrients: vitamins, minerals, trace elements [22]. Commercially produced feeding bags for parenteral nutrition however only contain macronutrients. Micronutrients have to be added (by a syringe). Only then can the so prepared mixture be administered to the patient. From a physiological standpoint, a bag supplying only macronutrients is ineffective; only when micronutrients are added, can hydrocarbons, protein and fats be effectively incorporated and transformed by the human body. Micronutrients are a component of many enzymes, hormones, carrier proteins and other substances which precondition the correct metabolism of macronutrients. Cases where any nutrient has to be excluded are rare and provisional, e.g. fats are excluded for treating chyle leak, vitamins A in liver insufficiency or copper and molybdenum in cases of cholestasis [23]. Complete nutrition mixtures are used routinely. An issue concerning settlements with the National Heath Fund (NFZ) may also be important. Lower valuations are made for incomplete feeding as compared to complete mixtures.

Palliative medicine, i.e. the time of difficult decisions

Parenteral nutrition in palliative medicine still arouses many controversies, and the decisions made at this time of a patient's life are the most difficult. In accordance with ESPEN guidelines, such support can be proposed to cachectic patients where feeding via the gastrointestinal tract is not possible, the patient agrees to such a procedure, and the estimated survival time is more than 2 months. On the other hand, these recommendations clearly state that PN should not be used to patients at the terminal phase of their life, only small amounts of fluids are to be sufficient, administered by the oral or subcutaneous route, and that the use of intravenous infusion is justified only by impairments

to consciousness due to dehydration [24, 25]. The meaning of the term 'palliative' has largely changed in the recent years, as it indeed it denotes a condition where healing is not possible, and where life can only be extended and the disease symptoms reduced. Now however this phase may last several years even, as in contrast to the term 'terminal'; meaning the last days, maybe weeks of life. For terminally ill patients, parenteral nutrition is contraindicated, and probably aggravates metabolic disorders and accelerates the patient's demise. If a patient, who is being nourished, enters the terminal phase, parenteral nutrition should be discontinued; in this situation, the patient no longer benefits from such a protocol [26]. For a patient in the palliative phase of treatment likely to survive at least 2 months, a decision to stop parenteral nutrition is difficult and is case-specific as always. Recommendations for PN usage do not differ from general recommendations. A malnourished patient, with good or average fitness (PS ≤ 2 or 3, improvable through symptomatic treatment), with a relatively stable disseminated malignant disease (without aggressive progression) and with relatively efficient organs, will benefit from such support. The last statement relates chiefly to the respiratory and blood circulation system, for instance patients with a massive exudation in pleural cavities, superior vena cava syndrome (SVCS) or massive metastases to lungs limiting respiratory capacity, or a patient with symptomatic heart failure, will not be candidates for parenteral nutrition. Hyperbilirubinemia with massive changes to the liver through metastases or through cancer spreading in the upper level of the abdominal cavity (pancreatic cancers, stomach cancers) poses a large problem; PN may strengthen cholestasis in this case. Nevertheless, the presence of kidney failure treated conservatively or with dialyses or the presence of diabetics in the insulin therapy phase, do not represent a major constraint in eligibility for PN if the above-mentioned problems are properly treated and tracked.

Summary

Clinical nutrition is one of the most significant pillars supporting oncological treatment, however, one has to be mindful of the cases where nutritional intervention, especially parenteral nutrition, does not bring benefits, and may even be harmful to a patient. Such cases include:

— PN for patients with a correct body mass and a correctly functioning gastrointestinal tract;
— PN due to hypoalbuminemia, in patients where feeding by the gastrointestinal tract is possible (orally or enterally);
— Lack of refeeding syndrome prevention for cachectic patients starting PN or EN;
— Use of feeding mixtures containing only soya oil as the sole fatty nutrient;
— Incomplete nutrition (macronutrients or micronutrients only);
— Classification of patients in the termination phase of cancer for PN undergoing persistent nutrition therapy.

Conflict of interest: none declared

Aleksandra Kapała, MD
Maria Skłodowska-Curie Cancer Center and Institute of Oncology
Department of Clinical Nutrition
Head and Neck Cancer Clinic
ul. Roentgena 5
02–781 Warszawa, Poland
e-mail: aleksandrakapala@interia.pl

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