

Review paper

## Importance of nutritional intervention for the therapeutic process of haematological malignancies

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### **ABSTRACT**

The incidence of malignancies, including haematological malignancies, is increasing among the world population. The most important issue is the fact that as a result of these malignancies, a patient involuntarily loses body weight which is caused by improper manner of nutrition and connected with it: postoperative complications, decreased response to treatment, increased risk of collapses, hospital-acquired infection and the increased risk of demise. Thus, one should strive to identify the nutrition disorders and that will enable to introduce a proper nutrition intervention and improve the clinic and therapeutic results. At the same time, it is crucial to arrange a diet therapy on the basis of the patient's current state of health, deficiencies and disorders, planned nutrition period and the possibility of preparation and consumption of specific meals.

**Key words:** nutritional intervention, patients, haematological malignancies

## INTRODUCTION

The incidence of neoplasm is increasing among the world population. According to the report of the World Health Organization, in the very 2012, 14.1 million of new cases were reported and there were 8.2 million of demises caused by malignancies [1, 2]. In Poland, the annual morbidity as a result of these diseases in years 1999–2014 increased by 42%, which was the cause of 24% demises among women and 27% demises among men in 2014 [3, 4]. Moreover, the data of the National Cancer Register show that in the last 3 decades there was over a double increase of haematological and lymphatic neoplasms.

Haematological malignancies constitute a very diversified group of diseases among which the most frequent ones are leukaemias (deriving from the cells of bone marrow – the white blood cells) and lymphomas (deriving from the lymphatic system). Leukaemias can be divided into myeloid and lymphocytic leukemias as well as chronic and acute leukemias. Lymphomas are divided into Hodgkin's lymphoma and non-Hodgkin lymphomas [5]. Haematological malignancies include multiple myeloma, MM, which is characterized by excessive multiplication of malignant plasmacytes [6]. These diseases occur in people at any time of their lives however with a higher age their risk increases. This is confirmed by the fact that patients with chronic lymphocytic leukemias or acute myeloid leukemias are on average above 65 years old [7, 8].

The patients with haematological malignancies are usually well nourished at the time of their diagnosis [9]. However, as the disease develops, the involuntary loss of body mass occurs which leads to a progressive malnutrition and complications connected with it [10]. In order to maintain the best possible nutritional state of an onco-haematological patient, it is necessary to have a proper nutritional treatment, apart from the proper medical therapy.

## REASONS OF BODY MASS LOSS THAT LEADS TO DISORDERS OF THE NUTRITIONAL STATE OF ONCO-HAEMATOLOGICAL PATIENTS

The loss of body mass connected with malignancies results most often directly from the decrease of the calorific value of the meals. It is the result of lack of appetite and an increased caloric need (which may result from the existence of the malignancy on its own or concomitant diseases) and also the malfunctioning of the gastrointestinal duct [10, 11]. The damage of the epithelium of the lower part of the gastrointestinal tract, which is caused by the prolonged inflammations, leads to the disorders of the con-

tents and as a results also the functions of the gastrointestinal microbiota. This, as a result leads, to a more frequent occurrence of diarrheas, increase of vitamin and mineral deficiencies and the increased presence of pathogenic bacteria [12]. The concomitant diseases, especially among the elderly patients, may lead to a body mass loss and increased intolerance to the administered treatment or even it may postpone its commencement. Thus, the concomitance of other disorders leads most often to an increased morbidity connected both with treatment (mainly by increasing the toxicity of the administered therapies) and with the disease [7, 13].

The occurrence of mental disorders connected with the disease, influencing among others the daily consumption of food, is also relevant. Patients who have malignancies also suffer from anxiety, depression, lack of energy, sexual dysfunctions, difficulties at work and the feeling of loneliness. All the above disorders lead to occurrence of a chronic stress, which according to results of the meta-analysis is connected with lower rates of survival and as a result an increased mortality [6, 7].

The endocrinological imbalance occurring in the course of the disease, connected with the increase of catabolic hormones (e.g. glucocorticoids) and the decrease of anabolic hormones (e.g. testosterone), may additionally increase catabolism and increase malnutrition [10] – similarly to the occurrence of metabolic disorders, closely connected with the general inflammatory state of the body. They are characterised by an increased breakdown of proteins and disorders of fat metabolism (the process of peroxidation of lipids) and carbohydrates (most of all an increased anaerobic glycolysis and glycogenesis) [14]. Factors which facilitate body mass loss may include intensification of inflammatory reactions as a result of the activity of proinflammatory cytokines produced by the cells of immune system and especially creation of reactive forms of oxygen (ROS, reactive oxygen species), whose long presence in the plasma hinders the proper functioning of the centers of hunger and satiety and at the same time leads to dysfunctions of nutrition [15, 16]. It is besides one of the reasons for an increased patients' demand for antioxidants [17]. On the other hand, despite the fact that excessive production of ROS and oxidant stress are commonly believed to be cancerogenic factors, they have an impact on the very cancer cells [16].

Additionally, anticancer treatment (chemotherapy and radiotherapy) may negatively influence the consumption of food due to fact that patients who undergo them may often have inflammation of mucous membrane, disorders of tasting and smelling and symptoms of problems with gastrointestinal tract (nausea,

vomiting, diarrhea, constipation) [10, 18, 19]. Depending on the emetogenic potential (force and frequency of causing vomiting) of chemotherapy, nausea and vomiting occur in 30–95% patients who undergo the treatment and they are believed to be the most cumbersome among the side effects. They may also occur during radiotherapy [20, 21]. Nausea and vomiting lead to occurrence of generalized exhausting symptoms which include among others anxiety, dizziness, excessive sweating, excessive saliva secretion or the feeling of satiety after consumption of small portions of food [18, 20, 22]. Such symptoms result in decreased quantity of life, impairment of the processes connected with regaining health and at the same time leading to patient's unfriendly attitude towards the therapy that he or she receives [19, 21].

### NUTRITIONAL IRREGULARITIES IN ONCO-HAEMATOLOGICAL PATIENTS

The state of nutrition of body, defined as a set of morphological, biochemical and functional features which directly or indirectly depend on the nutritional factors, plays the main role in maintaining health and its integrity [23].

Changes in nutrition of oncological patients occur with different frequency, depending mainly on the type, location and stage of malignancy. It also refers to patients with haematological malignancies [24]. It is estimated that this phenomenon occurs in 15–80% of patients with malignancies [23, 25, 26].

The main nutritional irregularities when it comes to patients with malignancies include malnutrition and cancer cachexia. According to the definition of malnutrition supplied by the ESPEN (The European Society for Clinical Nutrition and Metabolism), malnutrition is the effect of improper supply and/or impaired absorption or an increased loss of caloric and/or construction ingredients, which results in decreased body weight and changes of its composition (loss of fat tissue, decrease of fat-free body mass, relative increase of extracellular fluid which is caused by decrease of cellular mass). Then, the cancer anorexia-cachexia syndrome, referred to as CACS, is defined as a considerable and degenerative loss of body mass often connected with anorexia, metabolic irregularities and disorders in the composition of the body (among others greater loss of fat-free body mass than in the course of uncomplicated starvation) and systematic state of inflammation in the course of malignancy [27–29].

It has to be emphasized that malnutrition and the cachexia syndrome are connected with negative consequences in post-operative complications, decreased response to treatment, in-

creased risk of collapses, hospital-acquired infection and the increased risk of demise [29–33]. This is confirmed by the results of the research conducted by the patients above 60 years old with acute myeloid leukemia whose BMI (body mass index) < 25 kg/m<sup>2</sup> was connected with the increased risk of demise in comparison with patients with BMI > 30 kg/m<sup>2</sup> [34]. The analysis of the research conducted among 406 patients with the most frequent subgroups of non-Hodgkin's lymphoma – diffuse large B cell non-Hodgkin's lymphoma – showed that patients with underweight and obesity had worse prognosis than patients with proper body mass. It has to be added that different dependencies were observed with reference to sex and the age group of the surveyed people. Women > 70 years of age with the body mass index < 25 kg/m<sup>2</sup> had substantially lower chances of surviving than the ones with high BMI (> 25 kg/m<sup>2</sup>). On the other hand, women in the younger age group (< 70 years of age) who had lower BMI had a higher rate of surviving than the ones with high BMI. However, in the group of surveyed men there were no differences in the influence of BMI on the total surviving among the analysed age groups [35].

Malnutrition in patients with haematological malignancies may influence the effectiveness of treatment with the use of bone marrow and regeneration of haematopoietic system and immunological functions [24, 30]. It is also important that improper nutrition and malignant disease both influence each other: on the one hand, the occurrence of the malignancy leads to changes of nutrition and on the other hand, malnutrition or body impoverishment and cachexia have a negative impact on the course of treatment and further recuperation [10, 29].

In reality, identification of patients endangered by malnutrition enables a proper evaluation of the state of nutrition and nutritional intervention leading to improvement of clinical and therapeutic results. Thus, it seems necessary to evaluate the nutritional state of the patients with chronic diseases with special regard to patients with malignant diseases. There is no doubt that there is a wide range of methods which facilitate such evaluation. They are relatively easy to use, inexpensive and non-invasive. The most frequently used methods include: questionnaires evaluating the risk of malnutrition (PG-SGA, SGA, NRS 2002, MUST, MNA); nutrition interview (characteristics of the nutrition manner, evaluation of the caloric value and nutritional value of daily diet); anthropometric measurements (body mass fluctuations, waist and hip circumference, height and thickness of skin's folds); or the biochemical tests (albumin, prealbumin, transferase, total number of lymphocytes, nitrogen balance) [36, 37]. The bioelectrical impedance analysis (BIA) is also applicable in evalua-

tion of the patient's health state. At the same time, one needs to remember that each of these methods has both advantages and disadvantages and the diagnosis should not be based only on one tool but they should be used together as a supplement. Usefulness of the above listed tools is evaluated on their basis of predicting the proper clinic effects, such as: occurrence of complications, response to treatment, survival rate and the quality of life [25, 37].

## IMPORTANCE OF NUTRITIONAL INTERVENTION IN PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES

Anticancer therapy, especially regular application of chemotherapy cycles supplemented total body irradiation (TBI) and/or hematopoietic stem cell transplantation (HSCT) leads to dynamic changes and interruptions regarding the digestion and absorption of foods. Thus it is needed to introduce nutrition that is aimed at supplementing all nutrients with simultaneous tolerance by the patient's body [38].

The most proper method of nutrition is enteral nutrition (EN) by which the food is supplied orally and the oral nutritional supplements (ONS) are given and G-Tubes and nutritional stomas (gastrostomy and jejunostomy). When at least 60% of the daily caloric demand cannot be supplied by the gastrointestinal tract, one should consider enteral nutrition and parenteral nutrition (PN). However, the total parenteral nutrition (TPN) should be used when it is impossible to deliver nutrition in any other ways. *Nutritional standards of treatment in oncology* present a full scheme of the choice of nutrition manner of a patient and it is undoubtedly one of the basic elements of the therapy [11].

### Oral nutritional supplements

Oral nutritional supplements are currently used as a therapy supporting the patient both in the course of the malignant disease, its treatment and patient's convalescence. These supplements are recommended to all patients whose oral diet does not allow to cover the daily caloric demands. There are complete and incomplete, standard and specific products of ONS type to choose from. Moreover, they are divided into hypocaloric (0,5–0,9 kcal/ml of diet), isocaloric (1,0–1,2 kcal/ml) and hypercaloric (1,3–2,4 kcal/ml), and also polymeric, oligomeric and monomeric. In oncology, the most frequently used diets are the polymeric ones which include particles of proteins, polypeptides, maltodextrin, fatty acids, vitamins and minerals [39]. Moreover, the hypercaloric diets, whose main advantage is the fact that their small volume delivers high caloric and energetic value, are often applied [37]. Only a well-chosen diet based on the oral nutritional supple-

ments will not discourage the patient from using such products and it will not increase malnutrition neither will it cause additional ailments.

### Enteral and parenteral nutrition

Enteral nutrition is recommended when the patient is unable to swallow or has an increased inflammatory state of mucosa membrane of the gastrointestinal tract. Depending on the recommendations, the food may be supplied to stomach or small intestine. In each of these cases, one has to use ONS products because the ordinary home-made meals may contain some improper ingredients or proportions and as a result may be unsuitable for the patient. The choice of parenteral nutrition due to some possible complications should be made when nothing else helps. The matter is totally different when feeding via gastrointestinal tract is insufficient and the parenteral nutrition is only its supplement. All nutrients (amino acids, glucose, fats, electrolytes, vitamins and microelements) in parenteral nutrition are supplied by means of nutritional mixtures directly to the circulatory system with the use of venous catheter or cannulas [40]. Systematic description of the mentioned nutritional treatment exceeds the scope of this paper and it will be the subject of subsequent projects.

### Ailments connected with used therapy

The symptoms strictly connected with nutrition such as: nausea, vomiting, constipation, the side effects of the therapy, cause the decrease of the nutritional consumption and as a result lead to a worse nutrition and the quality of patient's life [41, 42]. The analysis of the results of the conducted research on the onco-haematological indicates that on average 23–37% of patients do not accept the recommended manner of nutrition [43, 44]. Additionally, malnourished patients more often report: loss of appetite, nausea, constipation, changes in the oral cavity, taste disorders, queasiness connected with smell and ailments connected with pain [44].

In order to alleviate these symptoms the pharmaceutical treatment is used most frequently, yet the diet therapy may also be useful. In case of nausea and vomiting, it is crucial to supply easy to digest, small in volume, cold and slightly fragrant meals. Meals in liquid form with electrolytes are often used [11]. Moreover, one should avoid skipping meals and consume them before the occurrence of hunger because it may increase the ailments [19]. In case of diarrhea, the procedure mainly consists in using constipating products such as white rice, wheat bakery products, cooked root vegetables or bitter tea and in oral supplementation of water and electrolytes [11].

### Substances with immunomodulating effect

Malignant cells may develop thanks to avoidance of the attack by the patient's immune cells and at the same time by impeding the immune system. It is gradually impaired by the growth of tumor and the metastases that may appear [45]. Thus, the haematological malignancies are often concomitant with different groups of deficiencies of immunity. Moreover, many procedures applied in these diseases, including the hematopoietic stem cell transplantation, chemotherapy, radiotherapy, lead to occurrence of secondary immunodeficiency and as a consequence an increased development of infections [46, 47]. As a result, it is necessary to use the immunomodulating substances which include among others omega-3 fatty acids ( $\omega$ -3), arginine and glutamine [37, 38, 48], yet the use these substances still arouses controversy, especially due to insignificant and contradictory results of the analyses. Moreover, the most frequently examined group still includes critically ill who among the oncological patients constitute only a subgroup.

Polyunsaturated fatty acids are present in the process of growth and differentiation of cells and they influence the inflammatory and immune processes. Omega-3 fatty acids limit the inflammatory reaction and the derivatives of omega-6 fatty acids are characterised by the opposite effect. According to the conducted analyses, among the mediators which decrease the inflammatory process one may differentiate 4 derivatives of fatty acids: arachidonic acid (AA;  $\omega$ -6), eicosapentaenoic acid (EPA;  $\omega$ -3), docosahexaenoic acid (DHA;  $\omega$ -3) and eicosapentaenoic acid  $\omega$ -6 (DPA- $\omega$ 6;  $\omega$ -6) [49]. The research conducted on the cell lines of the multiple myeloma (MM) proved that the EPA and DHA acids stimulate apoptosis in the cells of multiple myeloma which is closely related to gene expression engaged in different signal transductions. Moreover, the sensitivity to polyunsaturated fatty acids seems to be specific for the MM cells because the EPA and DHA do not influence the proper cells of peripheral blood. The authors also claim that supplementation or combined therapy with sensitivity to polyunsaturated fatty acids in chemotherapy of multiple myeloma may help to alleviate the resistance to chemotherapeutical medicine [50]. It is essential, however, that the conducted meta-analyses among the critically ill patients did not confirm the beneficial influence of omega-3 acids, regardless of the manner of their application [51–53].

It is postulated that glutamine, which is the precursor of glutathione, substance which is an antioxidant, in an indirect way participates in the decrease of the inflammatory reaction of the body [32, 48]. It is also the metabolic reactant of many rapidly proliferating cells, such as enterocytes and immune cells. Ad-

ditionally, it has the function of the intestinal barrier, it delivers energy to lymphocytes and neutrophils and it stimulates the synthesis nucleotide [54]. Meta-analysis carried out by Tao and others showed "moderate" evidence that the glutamine supplementation decreases the risk of infections and shortens the mechanical ventilation period in patients. "Little" evidence was also obtained regarding the length of stay in hospital [55]. On the other hand, the newest results of the 2 multicenter studies REDOX and MetaPlus – their authors draw conclusion that application of glutamine to patients critically ill is harmful [56, 57]. At the same time, the authors move for the necessity of conducting further research before joining the therapy [58].

The beneficial effects of supplementation with arginine include among others: immunological action, detoxication of ammonia or improvement of wound healing. Moreover, the data show that arginine improves the immune functions and its shortage weakens the immune response, at the same time increasing the risk of hospital infections or postponing the process of wound healing [48, 59, 60]. However, neither the meta-analysis carried out by Marik and Zaloga in 2008, nor the one by the Canadian group in 2013 showed its impact on the morbidity, risk of infections of length of stay in a hospital [61, 62].

The authors of the quoted meta-analysis suggest that one should look at the presented conclusions with caution because the results of the qualified research for review are very often hard to interpret due to differentiation regarding the manner of conducting observation, way of supply of ingredients, group size or type of diseases selected for the research.

One should also remember about the possibility of occurrence of interaction between the administered anticancer medicine and vitamins, minerals or substances with immunomodulating effect [63, 64].

### Refeeding syndrome

Refeeding syndrome (RFS) is a life-threatening state, decreasing the metabolic and haematological disorders from the cardiovascular system, liver, kidneys and lungs. RFS occurs as a result of improper nutritional therapy in extremely malnourished people. The frequency of RFS among patients with malignancies amounts to about 25% [65]. The pathophysiology of the syndrome is still not fully discovered to this day. It is known, however, that during the intake of large amounts of food in patients who are seriously malnourished, the concentration of glucose and insulin secretion suddenly increases, leading to an overwhelming concentration of electrolytes with retention of sodium and water. The potential

clinical consequences of this phenomenon include the increased risk of heart failure, peripheral edema or intercellular redistribution of phosphorus, potassium and magnesium with complications hazardous to health, such as contractions or cardiac arrhythmia, which increase the possibility of a sudden death [66, 67]. Additionally, hypophosphatemia and general lack of phosphate influences production of ATP (adenosine triphosphate) which can cause weakening of muscles, rhabdomyolysis, impaired hematopoiesis with symptoms of anaemia and decreased amount of oxygen delivered to cells. As a result, the natural immunity is also decreased which increases the risk of infectious complications [67].

On the basis of the above, the experts recommend that the preliminary nutritional phase in the group of RFS risk was introduced gradually. The recommendations significantly differ from each other, however it is estimated that the safe range is 25% (for patients with the highest risk) to 75% of daily energy demand. Therapeutic proceedings are conducted from 3 to 7 days, increasing daily energy intake by 10–25% until the required daily demand is obtained. Moreover, for prophylaxis purposes one should constantly monitor the water-electrolyte and vitamin-mineral balances and the fluctuations of the body mass of the patient [65]. Bearing in mind the above, it is essential that the supply of a suitable type of diet therapy in case of onco-hae-

matological patients should be always based on the current state of health and nutrition of a patient, on shortages and disorders in his or her body, on the planned type of treatment and period of nutrition and the possibility of preparation and consumption of specific meals – thus it possibly should be individualised. Applying nutritional intervention prepared in such way, most of all well tolerated by the patient, will allow to deliver the food ingredients necessary for the proper functioning of the body.

## CONCLUSION

The vast majority of patients struggling with a malignancy, depending on its type and stage, undergo different types of procedures (among other surgeries, radiotherapy or chemotherapy) which are closely connected with many side effects. They may include: loss of appetite, sore throat, dry mouth, change of taste, vomiting, nausea, diarrhea, constipation and chronic tiredness. All the above side effects negatively influence the consumption of groceries which leads to loss of body mass and further consequences. The researchers who focus on this subject claim that in case of malnutrition, cachexia and their complications the best approach is the prophylactic one and not the therapeutic one. Only as a result of identification of this type of disorders, the patient may receive a suitable diet therapy and at the same time it may enhance his or her medical treatment.

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