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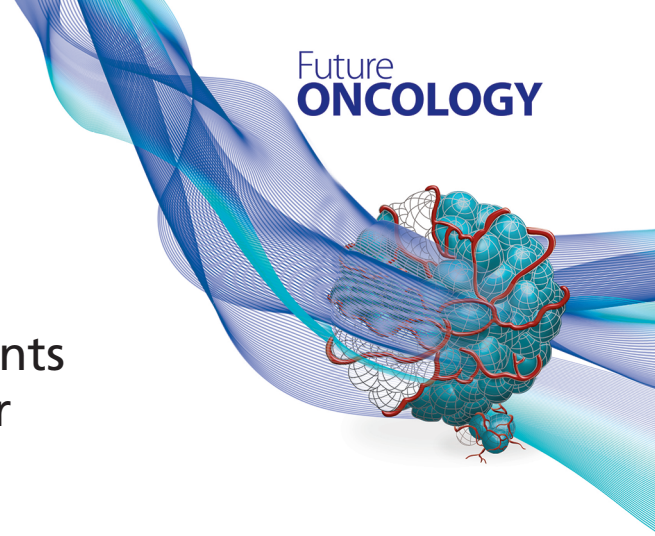

Enteral nutritional support in patients undergoing chemoradiotherapy for esophageal carcinoma

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Esophageal cancer patients are at a high risk of malnutrition. Both the disease itself and chemoradiotherapy will lead to the deterioration of nutritional status. The development of nutritional oncology promotes the application of enteral nutrition in tumor patients. Through nutritional support, prognosis is improved and the incidence of adverse chemoradiotherapy reactions is reduced, especially in those with head and neck or esophageal cancer. This review summarizes enteral nutritional support in esophageal cancer patients undergoing chemoradiotherapy in recent years, including a selection of nutritional assessment tools, the causes and consequences of malnutrition in esophageal cancer patients, types of access and effects of enteral nutrition. More patients with esophageal cancer will benefit from the development of enteral nutrition technology in the future.

First draft submitted: 2 March 2020; Accepted for publication: 6 August 2020; Published online: 28 August 2020

Keywords: chemoradiotherapy • enteral nutrition • esophageal cancer • nasogastric tube • percutaneous endoscopic gastrostomy • radiation esophagitis • self-expandable metal stents

Esophageal cancer is one of the most common gastrointestinal tumors in China. Its morbidity ranks 4th among all malignant tumors in men and 6th among women [1]. Because of its occult onset, most patients are diagnosed in the middle or late stage. For patients with unresectable locally advanced esophageal cancer, chemoradiotherapy is the preferred treatment and can effectively reduce local recurrence and distant metastasis, with a prolongation of survival [2]. However, mechanical obstruction caused by the tumor can lead to dysphagia, and radiation esophagitis causes pain when swallowing. In addition, gastrointestinal reactions to chemotherapeutic drugs result in symptoms of anorexia and vomiting, which lead to a lack of nutritional intake in patients [3]. Studies have shown that at least 60% of patients with esophageal cancer are suffering from malnutrition [4], causing decreased radiotherapy tolerance, delay or interruption of treatment. European Society for Clinical Nutrition and Metabolism guidelines suggest that oral nutritional supplements or tube feeding be considered to compensate for deficiencies in normal food intake. For patients with head and neck or esophageal cancer undergoing chemoradiotherapy, tube feeding can be used when swallowing is difficult. Because of inflammation of the oral and esophageal mucous membranes caused by radiotherapy, a percutaneous endoscopic gastrostomy (PEG) will be the first option [5]. Adequate nutritional support, especially enteral nutrition, plays an important role in maintaining organ function, improving immunity, reducing the incidence of complications and improving the prognosis of patients. This article briefly summarizes the enteral nutritional support in patients undergoing chemoradiotherapy for esophageal carcinoma.

Nutrition screening & assessment

At present, the commonly used nutritional screening tools in clinical practice are the Patient-Generated Subjective Global Assessment (PG-SGA), Mini Nutritional Assessment and Nutrition Risk Screening 2002 (NRS-2002) [6]. PG-SGA is recommended by the American Society of Parenteral Enteral Nutrition and has been used to evaluate other nutritional assessment tools. Patients with scores of 0–1 are well nourished, patients with scores of 2–3 are suspected to be malnourished, patients with scores of 4–8 have moderate malnutrition and patients with

scores above 9 are considered to have severe malnutrition. Nutritional intervention is required when the score is higher than 4, and emergency nutritional intervention is required with a score ≥9 [7–9]. PG-SGA includes a patient self-assessment and a medical staff assessment and is composed of seven parts: body mass, food intake, symptoms, activity and physical function, illness, stress state and physical examination. The first four parts are evaluated by the patients themselves, and the last three are evaluated by the medical staff. PG-SGA is used by clinicians, professional dietitians and patients and is highly specialized, sensitive and specific [10,11]. PG-SGA has the unique advantage of unifying a qualitative assessment and quantitative assessment, which distinguishes it from other nutritional assessment tools. However, its assessment workload is large and requires professionals and patients to carry out the assessment together; it is also highly subjective.

The Mini Nutritional Assessment is a nutritional status evaluation method established and developed in the early 1990s. The evaluation includes anthropometric measurements, including height, weight and weight loss; an overall evaluation, including lifestyle, medical treatment and disease status (digestive function status, etc.); a dietary questionnaire, including appetite, food quantity, meal times, nutrient intake and whether there are ingestion disorders; and a subjective evaluation, including subjective testing of health and nutritional status. This method is simple and feasible and has a good linear correlation with traditional human nutrition evaluation and human body composition evaluation methods [12]. However, it is less sensitive and requires patients to assess their own nutritional status, so it is not suitable for people with a lack of communication skills or those in developing countries with generally low educational attainment. The Mini Nutritional Assessment is suitable for nutritional risk screening in people over 65 years of age, but is not an appropriate tool for patients who cannot provide a reliable self-assessment, such as those with mental disorders, severe aphasia or severe acute illnesses such as pneumonia [13].

The NRS-2002 focuses on the nutritional status of patients and the severity of disease to assess the impact of nutritional interventions on clinical outcomes. The Chinese Society of Clinical Oncology expert committee on nutritional oncology has recommended NRS-2002 as the preferred tool for hospital admission nutritional screening. Its evaluation content mainly includes 3 aspects: malnutrition degree (0–3 points), severity of disease (0–3 points) and age ≥70 years old (0–1 point). The NRS-2002 has a higher positive detection rate of patients with nutritional risk than other methods and a higher specificity than PG-SGA and can be used as a reliable nutritional screening tool [14–16]. The total score of the NRS-2002 is between 0 and 7, and a score ≥3 indicates nutritional risk. Some foreign reports also indicate that lowering the nutritional risk score to ≥2 may be more beneficial for the nutritional treatment of patients with head and neck tumors [17].

In the opinion of the authors, NRS-2002 and PG-SGA can be flexibly applied to assess patients with unresectable locally advanced esophageal cancer. Most of these patients have significant dysphagia, which cannot be effectively alleviated in the short term under chemoradiotherapy treatment, and gastrointestinal reactions due to chemotherapy and radiation esophagitis due to radiation therapy further increase the difficulty of food intake and lead to malnutrition. Therefore, we should pay more attention to the deterioration of patients' nutritional status during treatment and implement nutritional interventions when necessary. When NRS-2002 is used to assess nutritional status, the patient's disease and age factors are available, and changes in height, weight or albumin can be recorded to provide a quick and intuitive response to any changes in nutritional status [17]. It should be noted that NRS-2002 can only judge whether there is nutritional risk, and the score does not determine the degree of nutritional risk. However, a high or low PG-SGA score can indicate the severity of malnutrition, and its assessment is more comprehensive and includes changes in body weight, food intake, symptoms, performance status and physical examination, which are highly correlated with a patient's prognosis [8]. Previous studies have shown that PG-SGA is associated with objective measures of nutritional assessment, prognosis and quality of life in advanced cancer [9,18–20]. When a patient's NRS-2002 score is ≥3, it indicates that the patient is at risk of malnutrition. If PG-SGA assessment conditions are available, such as professional personnel and clinical instruments, the PG-SGA score can be calculated to determine the severity of a patient's malnutrition so that appropriate nutritional interventions can be taken before or during treatment.

Malnutrition in esophageal cancer

Mechanisms of malnutrition

The mechanisms of malnutrition in patients with esophageal cancer are varied and include the disease itself and the secondary malnutrition caused by chemoradiotherapy. In terms of the impact of the disease, first of all, esophageal stenosis due to the presence of the tumor usually causes difficulty swallowing, which leads to special dietary requirements (patients can only eat a soft and semi-liquid diet), which reduces nutritional intake. Second, the

Table 1. Comparison of enteral nutrition access.

Access	Benefits	Risks	Suitable patients	Ref.
SEMS	• Safe and effective • Provide immediate relief from dysphagia	• Stent migration • Chest pain • Gastroesophageal reflux	Patients suffering from dysphagia due to esophageal stenosis, except those receiving chemoradiotherapy	[31,32]
NG	• Noninvasive • Convenient • Economical • Can operate at any time as needed	• Reflux esophagitis • Nausea and vomiting • Risk of tube blockage • Complications such as nasopharyngeal ulcers, bleeding, aspiration pneumonia	Malnourished patients during chemoradiotherapy using the NG tube shorter than 30 days	[6,33]
PEG/PRG	• Comfortable • Less interference with patients' lives • Large diameter, which can accommodate homogenate and is not easy to block	• Wound infection • Minor bleeding • Necrotizing fasciitis and peritonitis	Malnourished patients suffering from oral and esophageal mucosal inflammation due to radiation therapy	[5,34–36]

NG: Nasogastric; PEG/PRG: Percutaneous endoscopic gastrostomy/percutaneous radiologic gastrostomy; SEMS: Self-expandable metal stents.

cancer itself consumes a lot of nutrients in the process of development, and the basal metabolic rate of cancer patients is increased [21]. Third, systemic proinflammatory processes are activated, resulting in metabolic disorders of glucose, protein and fat. Systemic inflammatory responses are thought to be responsible for appetite and weight loss and may promote tumor development [5,6]. In terms of the impact of chemoradiotherapy, chemotherapy will cause gastrointestinal reactions, resulting in poor appetite and possibly vomiting, affecting the normal diet. In addition, toxic effects of radiation therapy, such as esophagitis, can cause or aggravate dietary disorders [22].

Consequences of malnutrition

Malnutrition results in poor adherence to treatment and reduces sensitivity to chemoradiotherapy. In addition, it affects short-term efficacy and prognosis, increases the toxicity of treatment, reduces quality of life and extends the length of hospital stays [5,23,24]. Malnutrition also causes sarcopenia, which is defined as a loss of skeletal muscle mass and strength [25]. Sarcopenia has been reported as an adverse prognostic factor for various cancers, including esophageal cancer [26,27].

Enteral nutrition access

Enteral nutrition is a way of providing nutrients and nutritional support for a patient's metabolic needs through the gastrointestinal tract. Nasogastric, PEG and percutaneous radiologic gastrostomy tubes are commonly used for enteral feeding. Self-expandable metal stents are also used to relieve dysphagia [28–30]. In clinical use, it is necessary to choose appropriate enteral nutrition access according to the patient's disease status so as to alleviate malnutrition and not affect treatment. A comparison between the three types of access is shown in Table 1.

Esophageal stent

In general, an unexpanded stent is placed under fluoroscopy about 3 cm above the tumor. When the stent is expanded, a patient's symptoms of dysphagia often immediately improve [31]. This can be used in patients with a strong desire for oral food. However, undergoing radiotherapy or chemotherapy after stent implantation increases the risk and severity of adverse reactions. Therefore, although self-expandable metal stent insertion can relieve obstructive symptoms, it should be avoided in patients who are likely to benefit from additional treatment with radiation or chemotherapy [37]. Some complications associated with stenting are also inevitable. This includes movement of the stent, incomplete expansion of the stent and excessive tumor growth and pain [32]. In addition, stents can cause gastroesophageal reflux. These common complications may make oral food intake more difficult, and recurrent dysphagia due to stent migration, tumor overgrowth or impaction of food can interfere with nutritional support. Studies have shown that when esophageal cancer patients use esophageal stents in the chemoradiotherapy process, chest pain is more intense and lasts longer, quality of life is poorer and albumin level is lower. Therefore, esophageal stents are mainly used for palliative treatment of dysphagia and are not suitable for tumors near the esophageal sphincter [34,38].

Nasogastric tube

If patients have severe dysphagia or progressive dysphagia before or during chemoradiotherapy, nasogastric tube insertion to avoid delay or interruption of cancer treatment can usually be performed. This method has a high success

rate and less procedure-related complications. Because the nasogastric tube is placed in the patient's nasopharynx, it can make it difficult to cough up sputum. Catheterization can also cause reflux esophagitis, and stomach stimulation due to the presence of the tube in the pharynx can increase the incidence of nausea, vomiting and aspiration [6]. A nasogastric feeding tube is thin and can admit only fluid, so it is not sufficient for nutrition. Therefore, it is mainly used for short-term nutritional support (generally <30 days) [33]. After each infusion, the tube should be rinsed with normal saline to prevent blockage. Patients with nasogastric feeding tubes have a relatively poor quality of life due to pain.

Percutaneous gastrostomy feeding

For patients whose treatment lasts longer than 30 days, a PEG can be selected. A PEG also interferes less with patients' lives and is more comfortable. Grilo *et al.* reported that the nutritional status of patients with unresectable upper esophageal cancer after enterostomy was basically stable, with few complications and no surgically related mortality [34]. In recent years, percutaneous radiologic gastrostomy has been developed as an alternative to PEG for esophageal cancer patients. Using computed tomography to guide percutaneous radiologic gastrostomy has several advantages. It accurately determines the position of the stomach and its position relative to the transverse colon or left lobe of the liver [39]. Computed tomography–guided percutaneous gastrostomy is also safer and leads to less trauma [40]. A patient can be fed 24 hours after the operation, and the gastrostomy fistula has a large diameter, which can accommodate homogenate and is not easy to block, so patients can be fed quickly and easily. In addition, a gastrostomy tube can be left indwelling for an extended period of time, so it can meet a patient's long-term feeding needs. At the same time, enteral nutrition through a gastrostomy tube avoids nasopharyngeal stimulation and reduces the occurrence of nausea, vomiting and esophageal reflux. Moreover, it increases the tolerance of enteral nutritional support and effectively improves the nutritional status of patients [41]. Previous studies have shown that gastrostomy has a low incidence of complications and improves survival with radiotherapy or chemotherapy but does not reduce obstructive symptoms or allow patients to take in enough food orally after the tube is removed [37]. In addition, gastrostomy is an invasive operation with a high cost and is difficult for patients to accept, and there may be complications, such as fistula infection [35,36].

Choice of enteral nutrition pathway

Each enteral nutrition pathway has advantages and disadvantages. In making the choice, we need to consider disease stage, degree of dysphagia and psychological and social factors. Therefore, decisions should be made with all members of the multidisciplinary nutrition team. Patients' needs for specific enteral nutrition pathways may change during different radiotherapy periods. It is important that doctors and dietitians make appropriate and timely adjustments to nutritional intake based on close monitoring of radiation toxicity, food intake and nutritional status [6].

Enteral nutrition effects

Previous studies have suggested that poor nutritional status is associated with chemotherapy-related myelosuppression. Patients with poor nutrition are more prone to hematologic toxicity, such as leukopenia [42]. At the same time, because of abnormal protein metabolism in patients with tumors, the synthesis of various proteins – albumin, prealbumin, transferrin, among others – in the liver is reduced, with these indicators being decreased to varying degrees [43]. Serum albumin level is a well-known indicator of nutritional status [44]. It is also a strong prognostic factor in patients with locally advanced esophageal squamous cell carcinoma [45,46]. Gibbs *et al.* pointed out that hypoalbuminemia can aggravate metabolic disorders, increase infection complications and prolong hospital stay, which is directly related to poor prognosis of patients and is an independent risk factor affecting prognosis [47]. Weight is the simplest, most direct and reliable indicator for nutritional assessment. Weight loss, which reflects changes in the balance of energy and protein, is common in esophageal cancer patients undergoing chemoradiotherapy. Jiang *et al.* found that 40.3% of patients with esophageal cancer lost ≥5% weight during radiotherapy, and weight loss was significantly correlated with the prognosis of patients with esophageal cancer undergoing chemoradiotherapy [48]. Therefore, clinical research involving enteral nutrition usually chooses height, body weight, BMI and blood nutrition indexes, such as serum albumin, prealbumin, hemoglobin and total lymphocyte count, as study endpoints [49–51].

Radiation esophagitis, pneumonia and myelosuppression are the most common side effects of chemoradiotherapy for esophageal cancer and seriously affect the tolerance and completion of treatment. Studies have shown that

supplementing nutrients can protect the integrity of gastrointestinal epithelium in patients undergoing radiotherapy, promote the proliferation of bone marrow, reduce the occurrence of high-level myelosuppression and reduce adverse reactions to radiotherapy [23,52].

Many studies have strongly confirmed the positive effects of nutritional interventions in improving the nutritional status of patients with esophageal cancer, reducing hematologic toxicity and gastrointestinal reactions and improving treatment tolerance and immune function. Sun *et al.* conducted a prospective study of 118 patients with unresectable advanced or metastatic esophageal cancer [53]. The patients were randomly divided into a nutrition group (received enteral nutritional support in addition to chemotherapy) and a control group (received chemotherapy alone). The results showed that the body weight, BMI and hemoglobin of the control group decreased significantly after chemotherapy ($p < 0.001$), whereas the nutrition group did not experience significant changes, except in hemoglobin. The incidence of grade 3–4 hematologic toxicity after chemotherapy in the nutrition group (15.4%) was significantly lower than that seen in the control group (42.1%; $p = 0.004$). Qiu *et al.* explored the effect of whole-course nutrition management on the prognosis and complications of concurrent chemoradiotherapy in patients with esophageal cancer [23]. Ninety-six patients were randomly divided into an intervention group (treated with whole-course nutrition management by the nutritional support team) and a control group (received general nutritional treatment). The results showed that there were significant differences in serum albumin and total protein between the two groups before and after treatment ($p < 0.05$). The differences in complications (such as radiation esophagitis, skin symptoms) and quality of life were statistically significant ($p < 0.05$). This study suggested that whole-course nutrition management is beneficial in patients with esophageal cancer undergoing chemoradiotherapy. Cong *et al.* reported that the prealbumin, transferrin and albumin parameters of patients in a nutritional support group were significantly better than those seen in patients treated with radiotherapy alone ($p < 0.01$), and the incidence of bone marrow suppression (20 vs 48%; $p = 0.037$) and infection (12 vs 44%; $p = 0.012$) was significantly lower than that seen in the control group [54]. In addition, only one patient in the nutritional support group did not complete the planned radiotherapy, whereas six patients in the control group interrupted or delayed radiotherapy. This study suggests that nutritional support may improve tolerance of chemoradiotherapy.

Conclusion & future perspective

A large number of studies have shown that the incidence of malnutrition in patients with malignant tumors is as high as 40–80%, and both the tumor itself and the therapeutic measures used to address the tumor can lead to the occurrence of malnutrition. About 40% of tumor patients die from malnutrition or its complications. Previous studies have pointed out that during concurrent chemoradiotherapy, patients with esophageal cancer can lose 5–10 kg of body weight [55]. Malnutrition in patients with esophageal cancer is prevalent, so it is necessary to improve the nutritional status of patients through nutritional support to ensure the successful completion of treatment and improve patients' quality of life. Nutritional therapy is the most basic and necessary treatment for cancer patients and is an important part of comprehensive treatment. European Society for Clinical Nutrition and Metabolism guidelines recommend that patients with esophageal cancer undergoing chemoradiotherapy receive enteral nutritional support to prevent treatment interruption [5]. Enteral nutritional support can relieve the suffering of patients, and it conforms to the physiological process. It also stimulates secretion of digestive juices, prevents intestinal dysbiosis and helps maintain mucous membrane structure and barrier function integrity. With the aid of enteral nutrition, the body's immunity is improved, which reduces the incidence of adverse reactions, and the treatment completion rate is improved. Therefore, enteral nutrition should become a method of enhanced nutritional support for patients with esophageal cancer.

With the development of nutritional intervention in clinical practice, oncologists have begun to pay attention to nutritional support for patients with tumors, especially head and neck tumors and esophageal cancer. In addition to nutritional support during treatment, home enteral nutrition has become common in Western countries, indicating that the concept of enteral nutrition has gradually been accepted by patients. Clinical nutrition research, including the relationship between nutritional support and prognosis and the application value of specific nutrients, is becoming a hot spot. In the next 5–10 years, more clinical studies of nutrition in oncology will be reported, which will provide more evidence for nutritional support in esophageal cancer patients undergoing chemoradiotherapy. At the same time, enteral nutrition technology will continue to develop, and patients will feel more comfortable with the treatment process, with better treatment effect and fewer side effects. More cancer patients will benefit from this, increasing their survival time and improving their quality of life.

Executive summary

Background

- Esophageal cancer patients undergoing chemoradiotherapy are at a high risk of malnutrition. European Society for Clinical Nutrition and Metabolism guidelines state that patients with head and neck or esophageal cancer may receive nutritional supplements such as tube feeding. Enteral nutrition plays an important role in maintaining organ function, improving immunity, reducing the incidence of complications and improving prognosis.

Nutrition screening & assessment

- The commonly used nutritional screening tools in clinical practice are the Patient Generated-Subjective Global Assessment (PG-SGA), Mini Nutritional Assessment and Nutrition Risk Screening 2002 (NRS-2002).
- PG-SGA includes a patient self-assessment and a medical staff assessment. Nutritional status deteriorates as the score increases. PG-SGA has the unique advantage of unifying a qualitative assessment and a quantitative assessment, which distinguishes it from other nutritional assessment tools.
- The Mini Nutritional Assessment is simple and feasible and has a good linear correlation with traditional human nutrition evaluation and human body composition evaluation methods. It is less sensitive and not suitable for people with mental disorders or a lack of communication skills.
- NRS-2002 is recommended by the Chinese Society of Clinical Oncology expert committee on nutritional oncology as the preferred tool for hospital admission nutritional screening. Its evaluation content includes malnutrition degree, severity of disease and age. The total score of the NRS-2002 is between 0 and 7, and a score $\geq$3 indicates nutritional risk.
- NRS-2002 and PG-SGA can be flexibly applied to assess patients with unresectable locally advanced esophageal cancer. When the NRS-2002 score is $\geq$3, the PG-SGA score can be calculated to determine the severity of the patient's malnutrition so as to take appropriate nutritional interventions before or during treatment.

Malnutrition in esophageal cancer

- The mechanisms of malnutrition in patients with esophageal cancer are varied and include the disease itself and the secondary malnutrition caused by chemoradiotherapy.
- Malnutrition results in poor adherence to treatment and reduces sensitivity to chemoradiotherapy. In addition, it affects short-term efficacy and prognosis, increases the toxicity of treatment, reduces quality of life and extends the length of hospital stays.

Enteral nutrition pathways

- Enteral nutrition pathways include nasogastric, percutaneous endoscopic gastrostomy and percutaneous radiologic gastrostomy. Self-expandable metal stents are also used to relieve dysphagia.
- Self-expandable metal stent insertion can immediately improve symptoms of dysphagia but is not suitable for patients receiving chemoradiotherapy. Complications associated with stenting are stent migration, chest pain and gastroesophageal reflux.
- A nasogastric tube can be used shorter than 30 days for nutritional support in malnourished patients before or during the chemoradiotherapy. Complications such as nasopharyngeal ulcers, bleeding and aspiration pneumonia may occur due to tube insertion.
- Percutaneous endoscopic gastrostomy and percutaneous radiologic gastrostomy avoid stimulating the nasopharynx and reduce the occurrence of nausea, vomiting and esophageal reflux. A gastrostomy tube can remain indwelling for an extended period of time, so it can meet a patient's long-term feeding needs. However, gastrostomy is an invasive operation with a high cost and is difficult for patients to accept.
- Each enteral nutrition pathway has advantages and disadvantages. In making the choice, we need to consider disease stage, degree of dysphagia and psychological and social factors. Patients' needs for specific enteral nutritional pathways may change during different radiotherapy periods.

Enteral nutrition effects

- Common nutritional assessment indicators include height, body weight, BMI and blood nutrition indexes, such as serum albumin, prealbumin, hemoglobin and total lymphocyte count.
- Radiation esophagitis, pneumonia and myelosuppression are the most common side effects of chemoradiotherapy for esophageal cancer.
- Many studies have strongly confirmed the positive effects of nutritional interventions in improving the nutritional status of patients with esophageal cancer, reducing hematologic toxicity and gastrointestinal reactions and improving treatment tolerance and immune function.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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