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Narrative Review

Nutritional Supplementation during Cancer Treatment: Is It Necessary, Safe and Helpful?A Narrative Review

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ABSTRACT

Cancer (CA) occurs when cells divide out of control. CA cells usually tend to spread from the initial locus to the near and far tissues, the so-called metastasis. The cause of most cancers is unknown to date yet some factors including viruses, ionizing radiations and certain nutritional factors may promote genetic changes leading to malignant tumor growth. There are several treatment options for cancers including surgery, chemotherapy, radiotherapy and immunotherapy. Although most cancers are life threatening, CA treatments carry many side effects for the affected patient including fatigue, anorexia, hair loss, anemia, neuropathy, gastrointestinal problems like diarrhea or constipation, and weight loss mostly due to loss of lean body mass. As many patients under CA treatment are not able to have an adequate dietary intake, using nutritional supplements (NS) may seem a reasonable approach. Nevertheless, there is some evidence suggesting that some NS may promote CA cell growth and poor prognosis. Here, the most recent findings in this field along with our personal experience are discussed and some recommendations are made based on current evidence.

Keywords: Nutritional supplementation, Cancer, Macronutrient, Micronutrient

Highlights

- As many patients under cancer (CA) treatment are unable to have an adequate dietary intake, using nutritional supplements may seem a reasonable approach.
- All in one (enteral) formulas and supplemental protein formulas may be used for those patients who cannot eat solid foods due to CA treatment complications.
- Antioxidant supplements including vitamins C, E and β-carotene may worsen the disease outcomes so they are not recommended.
- Calcium, vitamin D and ω-3 fatty acids/fish oil may be beneficial and can be prescribed whenever needed without any serious concern about interference with treatment.
- Multivitamin supplementation is possible when necessary in amount not exceeding RDA.

Abbreviations

BCAA: Branched chain amino acid
CA: Cancer
CRC: Colorectal cancer
Crn: Carnitine
DHA: Docosahexaenoic acid
EPA: Eicosapentaenoic acid
ESAs: Erythropoiesis-stimulating agents MN: Micronutrient
Gln: Glutamine
HMB: β-Hydroxy β-methyl butyrate
LC: L-Carnitine
MNA: Mini nutritional assessment
MUST: Malnutrition universal screening tool
PEG: Percutaneous endoscopic gastrostomy
RDA: Recommended dietary allowance
SES: Socioeconomic status

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Introduction

Cancer (CA) is the leading cause of death after cardiovascular disease (1). Although the main risk factor to global cancer burden in 2019 was behavioral, metabolic risk factors had a dramatic increase during 2010-2019 indicating that decreasing exposure to these modifiable risk factors will reduce CA morbidity and mortality rates globally (2). It is noteworthy that CA burden has increased in all socioeconomic status (SES) categories since 2010 but the increase was higher in low and middle SES groups (3).

CA occurs when cells divide out of control with the tendency to spread to other tissues near and far or metastasis. The cause of most cancers is unknown to date yet some factors including viruses, ionizing radiations and certain nutritional factors may promote genetic changes leading to malignant tumor growth. High rate of the malignant cell division brings about increased metabolic rate and nutrient deprivation of normal cells. These changes are commonly accompanied by augmented inflammatory response and negative protein-energy balance leading to massive weight loss mostly due to loss of lean body mass, the condition is called cancer cachexia (4).

There are several treatment options for CA including surgery, chemotherapy, radiotherapy and immunotherapy. Nevertheless, the treatment itself may impose a wide spectrum of side effects amongst them are fatigue, anorexia, changes of bowel habits, anemia, infections, hair loss, nausea and vomiting, loss of taste, dry mucosal membranes and neuropathy (5). These complications even deteriorate patient's nutritional status. There is evidence suggesting low nutritional status is associated with poor CA prognosis (6). As many patients under CA treatment are not able to have an adequate dietary intake, using nutritional supplements may seem a reasonable approach. Here, macronutrient and micronutrient (MN) supplementation and their impacts on CA patients are discussed.

Macronutrient Supplementation

Dietary supplements can be either protein or all in one (enteral) formula each of which has specific applications, advantages and limitations. Some studies have examined the effect of amino acids, ω-3 fatty acids and fish oil supplementation, as well.

(i) Protein and amino acid supplements

Protein

According to the ESPEN[1] guideline, protein requirement of patients with CA is 1.2-1.5 $g.kg^{-1}.d^{-1}$ and 2.0 $g.kg^{-1}.d^{-1}$ is associated with positive protein balance (7). Notwithstanding, those patients under CA treatment notably chemo- and radiotherapy may not be able to have a varied diet for one reason or another. They may receive near to adequate energy from soft and liquid foods mostly composed of carbohydrates but poor in protein. In these patients protein supplements may help preserve muscle mass and improve the quality of life, as documented in a very recent experimental study (8). In a multicenter clinical trial on 51 female subjects under CA treatment, whey protein isolate supplementation increased the amount of energy and protein intake as compared with those who received only nutrition counseling. Of those received protein supplement, only 4.6% showed gastrointestinal (GI) complications as diarrhea or constipation (9). Along the same line of evidence, in a study on 57 subjects with colorectal cancer (CRC), the effect of whey supplementation was evaluated initially, after 3 and 6 months of chemotherapy using body composition analysis, CT scan, mini nutritional assessment (MNA) and malnutrition universal screening tool (MUST). Finally, the results indicated that whey protein supplementation improved nutritional status and prevented chemotherapy toxicity significantly (10).

Branched chain amino acids (BCAAs)

BCAAs leucine, isoleucine and valine promote protein synthesis in the muscle but their possible effects on preservation of muscle mass in CA is still under investigation. Chemotherapy drugs interfere with BCAAs and muscle protein metabolism (11, 12). Therefore, it is difficult to anticipate the fate of supplemental BCAAs in this context. A recent systematic review documented that in just two studies, BCAAs supplement decreased unintentional weight loss due to chemotherapy while BCAAs-induced growth of cancerous cells is still a serious concern (13).

β-Hydroxy β-methyl butyrate (HMB)

HMB is a metabolite of an essential branched chain amino acid leucine that is thought to have anti-proteolytic property (14). The results of studies on HMB supplement effects in CA patients, despite promising observations in animal models (15, 16), have been controversial. In a multicenter trial on 38 subjects with lung CA, the participants showed a poor compliance of HMB-arginine (Arg)-glutamine (Gln) supplement so the study could not be concluded. Meanwhile, no evidence of alleviation was observed in those who consumed the supplement (17). Although a recent systematic review indicated that HMB supplementation has beneficial effects on muscle mass and function in the subjects with CA, the evidence to support this notion is limited at present (18).

[1] European Society for Clinical Nutrition and Metabolism (Formerly European Society for Enteral and Parenteral Nutrition)

Glutamine (Gln)

Gln, a non-essential amino acid and the amide form of glutamic acid, has many biological functions including contribution to muscle protein synthesis. Although early studies on the effect of Gln supplementation as an adjunct approach to chemotherapy showed no additional benefit (19), more recent studies documented the ameliorating effect of supplemental Gln in chemotherapy-induced mucositis (20) and chemo-radiotherapy-induced esophagitis (21). It is noteworthy that CA cells are highly dependent on Gln for their survival and Gln synthetase has been proposed as a therapeutic target in malignancies (22-24).

L-Carnitine (LC)

LC, β-hydroxy γ-N-trimethyl butyric acid, is a natural compound synthesized in body. LC, as a shuttle system, is involved in fat metabolism. Consequently, it is thought that LC supplement may help nourish muscles and prevent wasting during CA treatment. In a randomized multicenter clinical trial, a daily dose of four grams of LC for twelve weeks in 36 subjects with advanced pancreatic CA, significantly improved body mass index (BMI), nutritional status, quality of life and survival of the intervention group, as compared with the controls (25). Along the same line, in a clinical trial on eleven subjects with CA under chemotherapy, 1500 mg/d LC reduced general fatigue (26). Nevertheless, findings from a meta-analytical study did not support LC-supplementation as an approach against CA-related fatigue (27).

Creatine (Crn)

Crn is a naturally occurring compound synthesized in body from three amino acids arginine, methionine and glycine and is involved in energy supply to the muscles. Some experimental studies supported the anti-CA effects of Crn (28, 29). Nevertheless, there is limited evidence for the beneficial effects of Crn supplementation for lean body mass of CA patients (30). Moreover, emerging evidence indicates that Crn may promote CA metastasis (31).

(ii) All in one (enteral) formula

In the subjects with CA who are not able to take in solid foods for any reason, all in one formula can improve total energy and nutrients intake. In a trial on 15 subjects with progressive pancreatic and bile duct CA, eight weeks supplementation with two packs of nourishing formula (Medifood Miniwell OS, Korea Medical Food, Seoul, Korea; containing 200 kcal energy, 9 g protein, 6 g fat, 29 g carbohydrate; P: F: C = 17.5: 26.2: 56.3, % kcal; and 2.5 g fiber per pack =150 mL) resulted in a significant improvement of nutritional status. However, this improvement was due to increment of fat mass and/or maintenance of body composition. Besides, the intervention was more effective in the first run of chemotherapy and reduced treatment-induced fatigue (32).

(iii) ω-3 Fatty acids

The net effect of ω-3 supplements during CA treatment is debatable. Based on animal model experiments and analysis of circulating fatty acids concentrations in 118 CA patients undergoing treatment, the investigators recommended avoidance of fish oils or oily fishes herring and mackerel consumption before and during chemotherapy as it may induce chemoresistance against cisplatin (33). Nevertheless, this notion was seriously criticized (34, 35). On the contrary of those findings, daily consumption of 2g fish oil containing 0.6 g eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) for nine months in CRC patients under chemotherapy (n=15) resulted in a significantly longer time of tumor progression compared with the controls (36). A systematic review concluded that ω-3 supplementation in the subjects with CA undergoing chemo- and/or radiotherapy may help preserve their body composition (37).

Micronutrient supplementation

CA treatment adversely affects patients' dietary intake, macro- and micronutrient status (38-40). Nevertheless, the effect of MN supplementation is controversial.

Antioxidants

The most common antioxidant preparations are vitamins C and E, β-carotene and flavonoids including green tea catechins. Several anticancer drugs act through generating reactive oxygen species (ROS) and inducing oxidative stress. Consequently, the circulating concentrations of the antioxidants may decrease. Nevertheless, consuming antioxidant supplements may interfere with chemotherapeutic agents (41, 42). A large study on 2,223 post-menopausal female subjects with non-metastatic breast CA found a significant association between antioxidant consumption during chemo- or radiotherapy and deteriorated CA prognosis (43). As for vitamin E, at least two clinical trials on subjects with head and neck CA reported that consumption of 400 IU a day of α-tocopherol was associated with higher risk of tumor relapse and decreased CA-free survival (44, 45).

Several lines of evidence indicate anti-cancer effects of green tea catechins (46, 47). Though consumption of green tea during CA treatment is commonly considered safe (48), evidence from human studies is still too limited to recommend green tea catechins supplements during chemo-radiotherapy.

Other vitamins and minerals

Calcium and magnesium supplements may be prescribed to the subjects under CA treatment without a serious concern about possible interactions. Magnesium supplementation may reduce chemotherapy-induced peripheral neuropathy in CRC patients (49). Zinc supplementation may be prescribed in those patients who are zinc-deficient and unlikely to get enough from their diet (50). Although zinc supplementation may be beneficial in preventing radiotherapy-induced oral damage, it does not seem to alleviate chemotherapy side effects (51). Oral iron supplement is not usually recommended during CA treatment. A large study on 1,134 female subjects with breast CA revealed that those who were taking in iron supplement during chemotherapy were more likely to have relapse or die of any cause (52). Nevertheless, in those patients receiving erythropoiesis-stimulating agents (ESAs) to treat chemotherapy-induced anemia, addition parenteral iron to ESAs may improve hemoglobin response and hence reduce the need for transfusion (53). Current evidence suggests that vitamin B_{12} supplement during CA treatment is not associated with adverse outcomes but supplementation both before and during chemotherapy may increase mortality (52).

Among vitamins, vitamin D is unique in many aspects including its endogenous biosynthesis and limited dietary sources (54). Vitamin D metabolism may be dysregulated in many forms of malignancies leading to vitamin D deficiency (55). Besides, CA treatment especially chemotherapy may decrease circulating concentrations of 25-hydroxycalciferol (25(OH)D), the most abundant form of the vitamin in body (56). Vitamin D supplementation during CA treatment not only brings serum 25(OH)D back to normal (56), but may improve survival in the subjects with CA, as well (57). Although there is strong evidence for antioxidant properties of vitamin D (58-61), and antioxidant supplements may interfere with chemotherapeutic agents (41, 42), this is not a serious concern with vitamin D supplementation during CA treatment (57).

CA and its treatment may cause MN deficiency (40, 62), and many patients may not be able to receive adequate dietary intake for one reason or another (63). It is therefore plausible to provide the needed MN through supplementation. This can be done through selected MN supplementation or using multivitamins. As described earlier, the results of the studies on selected MN have been controversial and even some reported adverse outcomes (41-45). One of the reasons for these observations might be the doses used in most of these studies were above recommended daily allowances (RDAs). To support this notion, in a large study on the effect of supplement use on survival of female subjects with breast CA, even using vitamin B_{12}, commonly known harmless even in high doses (64), both before and during chemotherapy was associated with shorter disease-free survival. However, consumption of multivitamin was not associated with survival (52). It is noteworthy that the RDA for vitamin B_{12} in adults is 2.4 µg while the amount in the cyanocobalamine sublingual tablet and injectable preparation is 50 and 500-1000 µg, respectively. Along the same line, MN supplementation in the amounts not exceeded RDA has been suggested to be beneficial to improve nutritional status of the subjects with gastrointestinal CA (65). The results of a clinical trial of efficacy of Texidrofolico®, a nutritional supplement containing MNs, on patients with lung CA showed prevention of weight loss and reduction of chemotherapy adverse effects in the supplemented group (66).

Summing up

Current evidence leaves no room for doubt that nutritional intervention is preciously beneficial for CA patients (67, 68). The first choice to meet nutritional needs of the subjects under CA treatment, as of any other subjects, is through diet. Nevertheless, this may not be possible at least during one period. In these cases, we need to use macro- and micro-nutrient supplementation (Figure 1). It must be emphasized that provision of enough energy is the first priority in meeting the patients' nutritional needs mostly as small energy-protein-dense meals (7). In those patients who are not able to consume solid foods due to CA treatment complications, we do recommend to use supplemental all-in-one (enteral) formula. However, these formulas are usually a bit viscous and sweet so, for example, patients with head and neck CA with mucositis, esophagitis and similar complications of radiotherapy may not be able to consume enough. In these cases, high purity protein supplements are better tolerated as they are less viscous and sweet than enteral formulas. Energy may be provided to these patients by soft carbohydrate foods (like pasta) enriched with healthy oils. If none of these approaches are effective, tube feeding through PEG (percutaneous endoscopic gastrostomy) or jejunostomy may be proposed to both oncologist and the patient. Always keep in mind that no supplement will work miraculously in the context of energy deficit.

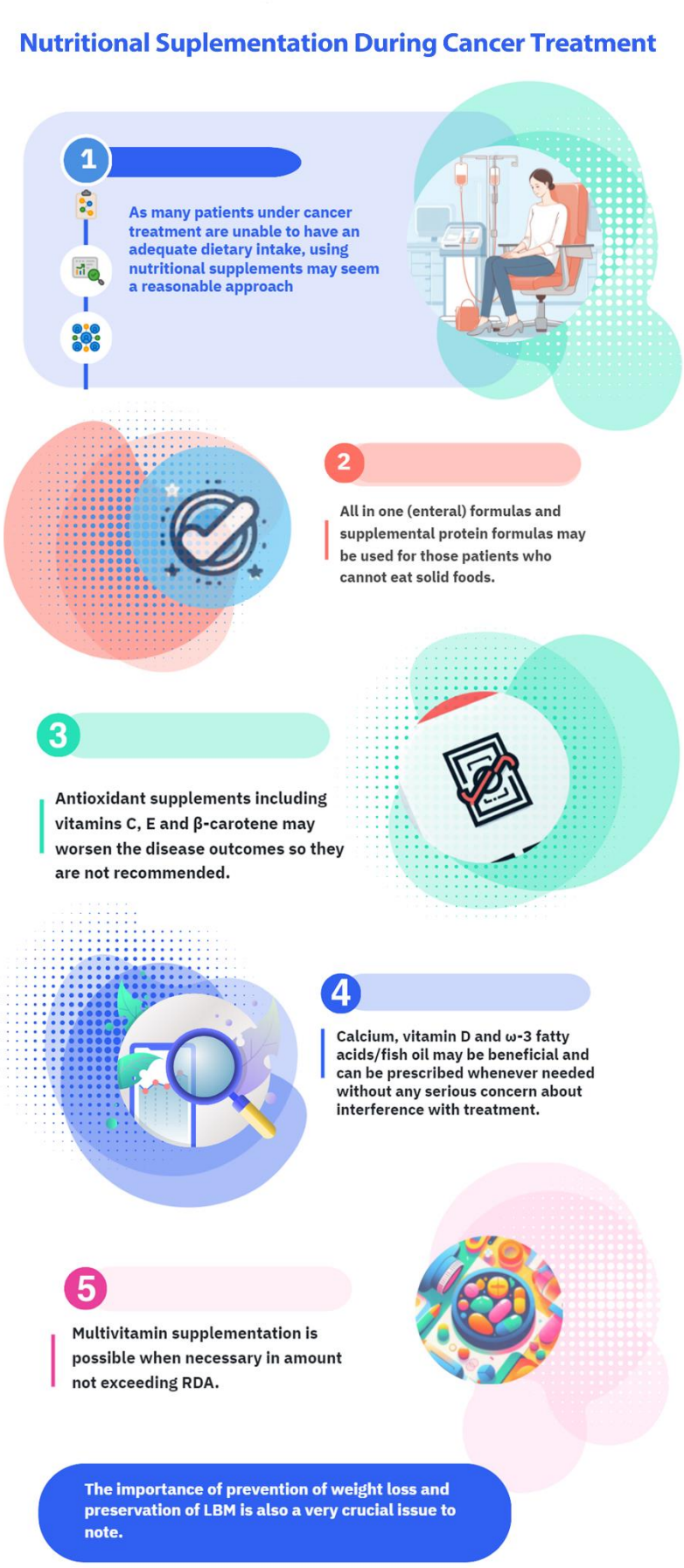

Figure 1. Nutritional supplementation in cancer patients at a glance

The efficacy of MN supplementation in CA patients is debatable. Many oncologists do recommend their patients not to use any kind of nutritional supplement during CA treatment. Notwithstanding, calcium, vitamin D and ω-3 fatty acids/fish oil can be prescribed when needed without any serious concern about interference with CA treatment. Other MNs can also be provided to the patients during CA treatment in the form of multivitamins based on individualized assessments and in the amounts not exceeding RDAs. Patients should be regularly assessed for any adverse effects of supplementation (69). The individualized dietary counseling and logical use of dietary supplements can improve patients' nutritional status quality of life and treatment tolerance in a cost-effective manner (70-74). After all, close relation with the oncologist and other members of CA treatment team for unanimity as well as very intimate and sympathetic individualized counseling with patient and his/her family members are necessary.

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